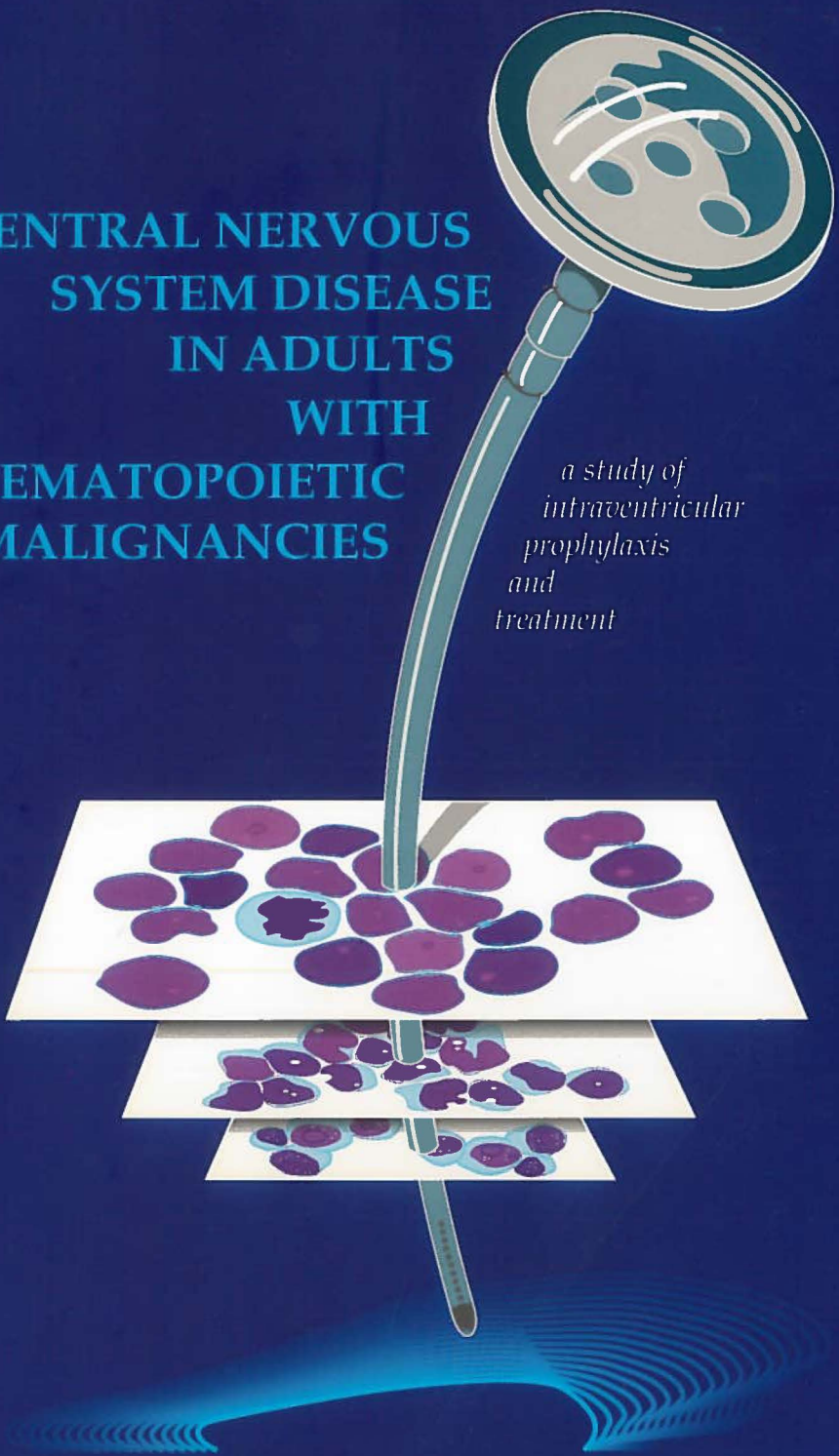
H. HAAXMA-REICHE

CENTRAL NERVOUS SYSTEM DISEASE IN ADULTS WITH HEMATOPOIETIC MALIGNANCIES

a study of intraventricular prophylaxis and treatment



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Stellingen behorende bij het proefschrift

CENTRAL NERVOUS SYSTEM DISEASE IN ADULTS WITH HEMATOPOIETIC MALIGNANCIES

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van H. Haaxma-Reiche

1. Een Ommaya reservoir behoeft niet verwijderd te worden om een hiermee in verband gebrachte bacteriële infectie (ventriculitis, meningitis) succesvol te kunnen behandelen.

   Dit proefschrift en

   Siegal T, Pfeffer MR, Steiner I. Antibiotic therapy for infected Ommaya reservoir systems. Neurosurgery 1988; 22:97-100.

2. Een bacteriële meningitis bij een leucopenische patient is moeilijk te diagnostiseren, daar de klassieke klinische symptomen en liquorafwijkingen volledig kunnen ontbreken. Een lichte verandering van de status mentalis of een geringe temperatuurverhoging hebben dan reeds een grote betekenis.

3. Een dreigende dwarslesie bestaat niet, een beginnende dwarslesie is wel bedreigend.

4. Bij metastatische epidurale ruggemergcompressie is van een initiële hoge dosis dexamethason (100 mg) geen beter resultaat te verwachten dan van de conventionele dosis (10 mg), wat betreft pijnbestrijding, ambulantie en blaasfunctie.

   Resultaten van een onderzoek van de Landelijke Werkgroep Neuro-Oncologie.

5. Dexamethason gegeven voor metastatische epidurale ruggemergcompressie behoort na het aanvangen van de definitieve behandeling geleidelijk gestaakt te worden. De totale medicatietijd dient niet langer te zijn dan 14-21 dagen.

6. Het binnen een oncologische polikliniek beschikbaar stellen van een spreekkamer aan een neuroloog moet als patientvriendelijk en kostenbesparend beschouwd worden.

7. Bij verdenking op een supratentorieel glioom is histologische bevestiging van de diagnose vereist, ongeacht de aan- of afwezigheid van aankleuring op het computertomogram na toediening van intraveneus contrast.

8. Een metabole encefalopathie veroorzaakt verwardheid bij de patient en nogal eens verwarring bij niet neurologisch geschoolde medici.

9. Was tot voor enkele jaren bij ernstig hersenletsel de neuroloog veelal betrokken bij het stellen van de indicatie tot beademing, thans behoort het steeds vaker tot zijn/haar taak vast te stellen wanneer deze (beter) beëindigd kan worden. Het is de vraag of dit altijd een verbetering inhoudt.

10. Podophyllotoxine derivaten (VP16-213, VM26) kunnen effectief zijn bij de behandeling van hersenmetastasen van het kleincellig lomgcarcinoom. Aan VM 26 moet de voorkeur gegeven worden.
    Haaxma-Reiche H, Berendsen HH, Postmus PE. Podophyllotoxins for brain metastases of small cell lung cancer. J Neuro-Oncol 1988; 6:231-232.

11. Zolang de resultaten van een prospectieve gerandomiseerde studie bij "solitaire" hersenmetastasen van solide tumoren niet bekend zijn, kan niet verantwoord gekozen worden tussen enerzijds uitsluitend radiotherapie en anderzijds neurochirurgische extirpatie met nabestraling. De keuzes die momenteel gemaakt worden, zijn vaak ad hoc beslissingen.
    Solitary brain metastasis treatment: a randomized trial.
    Neurology 1988; 38:suppl 1,393. Abstract by 20 authors from the Netherlands.
    Surgery for single brain metastases: a prospective, randomized trial.
    Neurology 1987; 37:suppl 1,308. Abstract by 7 authors from Lexington (KY), USA.

12. Het pallidum is van belang voor de snelheid van de voorbereiding en de uitvoering van een beweging.

13. Bij een wervelfractuur in het thoraco-lumbale overgangsgebied impliceert neurologische uitval een gecombineerd letsel van het voorste en het achterste complex.

14. Bij het voortgaan van adoptie van buitenlandse kinderen dient de ambulante en residentiële hulpverlening versterkt te worden.

15. Een overheid, welke de burger informeert over het vervagen der landsgrenzen in 1992, maar tegelijkertijd de gezondheidsvoorzieningen wil plannen volgens eeuwenoude provinciegrenzen, heeft het klaarblijkelijk moeilijk met de orientatie in tijd en plaats. Dit doet het ergste vrezen ten aanzien van de derde in dit trias, nl. de orientatie in persoon.
    oa.: Vaststelling plannen instellingen voor geestelijke gezondheidszorg in het kader Wet ziekenhuisvoorzieningen. Staatscourant 142 28-7-87, 8-10.
    Strub RL, Black WF. The mental status examination in Neurology. FA Davis Cy., Philadelphia, 1977, p 67.

16. Centrale pijn, daar lig je niet van wakker.

17. De verschillende fasen van de nieuwbouw van het Academisch Ziekenhuis te Groningen (AZG) bemoeilijken ieder op geheel eigen wijze een efficiente interdisciplinaire consultverlening.

RIJKSUNIVERSITEIT GRONINGEN

CENTRAL NERVOUS SYSTEM DISEASE IN ADULTS WITH HEMATOPOIETIC MALIGNANCIES

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Hanny Haaxma-Reiche

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CONTENTS

ABBREVIATIONS

A	doxorubicin (adriamycin)
ALL	acute lymphoblastic leukemia
AML	acute myelocytic leukemia
AraC	cytosine arabinoside
BM	bone marrow
BMT	bone marrow transplant
β_2m	beta-2-microglobulin
CBL	polymorph centroblastic lymphoma
CNS	central nervous system
CR	complete remission
CSF	cerebrospinal fluid
CT	computerized tomography
C x T	concentration x time
D	daunorubicin
DIC	disseminated intravascular coagulation
HC	hydrocortisone
HG	high grade
IBL	immunoblastic lymphoma
IG	intermediate grade
i.t.	intrathecal
i.v.	intravenous
i.vt.	intraventricular
LBL	lymphoblastic lymphoma
LDH	lactate dehydrogenase
LG	low grade
(M)CHOP	(methotrexate) cyclophosphamide doxorubicin vincristine prednisone
MenLy	meningeal lymphoma
ML	meningeal leukemia
MRI	magnetic resonance imaging
MTX	methotrexate
NHL	non-Hodgkin's lymphoma
NBTE	non-bacterial thromboendocarditis
NR	non responder
P	prednisolone
PB	peripheral blood
PR	partial remission
TG	6-thioguanine
V	vincristine
VP16-213	etoposide
WBC	white blood cells

CHAPTER 1

FACTS RELEVANT TO THE APPROACH OF MENINGEAL LEUKEMIA AND LYMPHOMA

1. INTRODUCTION

At the time that more effective systemic therapy for acute lymphoblastic leukemia (ALL) resulted in remissions and longer survival in adults, the development of meningeal leukemia (ML) in these patients became a serious problem. The considerable morbidity caused by meningeal leukemia induced the department of Hematology to consider carefully a reliable form of central nervous system (CNS) prohylaxis.

An implantable device for long-term access to the cerebrospinal fluid (CSF) was described in 1963 by Ommaya.[1] Although it was introduced for the treatment of fungal meningitis, the field of subsequent applications widened. In 1968 Ratcheson and Ommaya described the use of the "Ommaya" reservoir in 60 patients with different diagnoses.[2] Five of them had resistant ML. Positive results in ML were reported in a letter by Spiers and Booth in 1973. Caution was recommended in the prophylactic use of the reservoir, because of their initial rate of complications.[3]

The important observations by Shapiro et al. regarding the difference in distribution of methotrexate (MTX) after lumbar and ventricular injections led us to favor an intraventricular (i.vt.) approach.[4] The protocols for CNS prophylaxis and for treatment of ML and meningeal lymphoma (MenLy) were the result of the collaboration between the hematological, neurological and neurosurgical departments. The first Ommaya reservoir in our series was inserted in 1976.

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2. HISTORY

The first case of chloroma of the skull and dura mater was reported by Burns in 1811.[1] In 1885 von Recklinghausen expressed the idea that chloroma was a manifestation of leukemia.[2] The relationship between chloroma and leukemia was further elaborated by Dock (1893).[3] He included a description of the attachment of these tumors to the periosteum and the dura of the cranium and the vertebral column. Infiltration of the spinal cord with leukemic cells was seen by Rosenstein (1881) and focal accumulation of leukemic cells in association with the smallest bloodvessels in the brain and spinal cord was reported by Hirschlaff (1898) and Spitz (1901).[4-6] The involvement of the leptomeninges is cursorily commented upon by Critchley (1930) in an article on the spinal symptoms in chloroma and leukemia.[7] Secondary changes in the spinal cord due to compression by tumorous masses or due to infarction in the territory of obstructed bloodvessels were recognized by this author. He also observed the involvement of the spinal nerve roots. Schwab and Weiss (1935) called attention to the frequent finding of CNS lesions in leukemia.[8] Their literature review indicated cerebral hemorrhage as the leading lesion, but in their own patients cranial nerve involvement was the most frequent sign. Although examinations of the CSF were performed in only a few patients, they recognized the importance of the abnormal findings, such as elevated pressure and increased cell count and protein content. Leidler and Russell (1945) collected brain pathology studies in leukemia from the literature and added their own material.[9] They considered hemorrhage and leukemic infiltration occurring independently or together in the brain, the dura mater and the leptomeninges to be characteristic. One of the conclusions they deduced from their material was that hemorrhages in the brain were not only caused by thrombocytopenia, but also by leukemic infiltration. This observation was more precisely defined by Phair et al. (1964).[10] In their study a strong relationship existed between a high terminal white blood cell (WBC) count and significant parenchymal hemorrhage. They offered the following explanation. "Above 50.000 cells/mm^3 a significant effect on blood viscosity becomes evident. Immature cells are larger than the more mature forms and myeloid cells have a greater volume than comparable lymphoid cells. The effect on blood viscosity is accordingly." Indeed cerebral hemorrhage frequency was the lowest in chronic lymphocytic leukemia.[11] The increased blood viscosity results in stasis and subsequent vascular and tissue hypoxia and vasodilatation. Vascular permeability increases and ultimately leads to vascular necrosis and hemorrhage. A predilection for involvement of the cerebral white matter can be explained by the multiple small tortuous thin walled vessels in that region. In contrast thrombocytopenia is instrumental in the subarachnoid and subdural hemorrhages.

The introduction of chemotherapy in the treatment of leukemia around 1948 created a distinct shift in the neurological symptomatology. Shaw et al. (1960) described an increasing number of patients with clinical evidence of meningeal irritation and increased intracranial pressure in the absence of hemorrhage and infection. This syndrome was called meningeal leukemia and was related to infiltration of the arachnoid by leukemic cells.[12] The decrease of the above described picture of leukostasis and hemorrhage could be attributed to lower WBC counts in response to chemotherapy. The increase of meningeal leukemia was related to the longer survival of patients with acute leukemia and to the failure of the antimetabolites which were used at that time to cross the blood-brain barrier.

To review the literature on lymphoma is hindered by the lack of uniformity in nomenclature. Virchow (1863) is credited for making a distinction between "leukemia lymphatica" (leukemia) and "leukemia splenica" or "sarcoma lymphaticum" (lymphoma).[13] Over the years several classifications have been introduced to subdivide the non-Hodgkin's lymphomas (NHL). The latest are based on immuno-histo-pathologic standards and clinical behavior.[14] The first description of a lymphosarcoma invading the cranial dura and optic nerves was given by Mosler (1872), while epidural spinal involvement was recorded by Guillain et al. (1925).[15,16]

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3. PATHOGENESIS AND PATHOLOGY

The relationship between leukemia and CNS involvement was altered by the introduction of chemotherapy. The original picture was for the greater part determined by high WBC counts and thrombocytopenia. Since the availability of effective systemic therapy their occurrence was suppressed and this resulted in a shift to meningeal disease.

ANATOMY

The outermost of the meninges is the dura mater. The leptomeninges consist of the arachnoid and the pia mater. The brain and spinal cord are covered by the glia limitans. The pia adheres closely to the brain and the spinal cord. The arachnoid is positioned between dura and pia and forms trabeculae, through which vessels and nerves course. The trabeculae traverse the arachnoid space, which contains the CSF, and they join the pia. Wherever vessels enter or pass from the brain or cord, the pia and arachnoid enwrap them, forming a perivascular space, the so-called Virchow-Robin space. They surround the vessels except from the precapillary arteriolar level up to the postcapillary venular level.[1] The blood-brain barrier is formed by the tight junctions of the vascular endothelium. The circumventricular organs miss such a barrier. At these sites the endothelium has fenestrations. Forms of tight junctions, but also of gap junctions exist between the arachnoid cells. Tight junctions are present between cells close to the dura and also on the surface of the arachnoid, which is exposed to the CSF.[2]

CNS INVOLVEMENT IN UNTREATED LEUKEMIA

Reports from the earlier era provide some information about the unchecked process. Leukemic nodules or chloroma were seen, quite often attached to bony structures or dura. Foci of infiltration were present in the brain substance and these were frequently surrounded by hemorrhage. Infiltrates and bleeding could also be found in the dura and the leptomeninges. The concept how this picture evolved stems from several pathology studies.[3-5] Fatal intracerebral hemorrhages were associated with blastic crisis and a high WBC count, nearly always over $100 \times 10^9/l$. Chronological reconstruction of the encountered lesions read as follows: Collections of leukemic cells filled and obstructed small intracerebral vessels. These became dilated and leaky. Increased permeability allowed an exudate composed of fluid and malignant cells to appear, early on confined to the Virchow-Robin spaces.[6] Later the blood vessels were destroyed and leukemic nodules were formed. Not only the number of WBC, but also the variation in cell size in the different types of acute and chronic leukemias

influenced the process of leukostasis. Finally hemorrhage occurred in the nodules, leading to a fatal event. The hemorrhagic lesions were multiple, occurred at the capillary level and were almost exclusively confined to the white matter.[7] The influence of the number of platelets was limited. Although they were sometimes decreased, they had never fallen below $10x10^9/l$. In contrast fatal subarachnoid hemorrhage and acute subdural hematoma were uniformly associated with severe thrombopenia. Dural infiltration was much more frequent (70% of the cases) than arachnoidal involvement (30%).[3]

CNS INVOLVEMENT AFTER CELL REDUCTIVE TREATMENT OF LEUKEMIA

When the number of WBC is reduced by the use of cell reductive chemotherapy leukostasis will not occur, but other forms of invasion of the CNS are still possible.

Origin of leukemic cells in the brain and meninges

Several authors agree that leukemic cells can first be observed in the walls of superficial leptomeningeal veins and as dense perivenous infiltrates.[8-10] About the origin of these cells the opinions differ. This question has been addressed in several fashions. Analysis of human material and experimental animal work has cast some light on this issue. Possibilities to be considered are: by direct extension, metastatic, either by hematogenous spread or by the lymphatic channels, and de novo.

Direct extension

If dural invasion is found more often than arachnoid infiltration (see above) it could be that the first localization is the primary site. But from where did the leukemic cells invade the veins and surrounding space? Local hemorrhage was not observed and diapedesis could initially not be proven. In a few patients direct extension from the bone marrow of the skull to the dura was seen.[8] Migration to the arachnoid via perivascular and perineural tissue has been noticed in humans.[3] Later experiments in guinea pigs documented transendothelial passage of leukemic cells in the leptomeningeal veins, but direct proof of the direction of the cell migration could not be offered by this study, although the author suggested a centripetal route.[11] The preference for the dura was also favored by the observations in mice inoculated with L1210 leukemia cells. After intracerebral inoculations dural vein infiltrations were the earliest findings, with leptomeningeal invasion coming later. Subcutaneous inoculations caused extensive extracranial disease and small deposits in the arachnoid, which appeared to have reached this place by migration from the dura and the

bone marrow. The development of the arachnoid infiltration seemed a matter of time. Is this explanation enough? Probably not. Extension from dura to arachnoid and further in the brain parenchyma cannot be discarded completely, but it probably accounts for only a few cases nowadays.

Metastatic dissemination

Lymphatogenous spread: A limited lymphatic drainage system exists in the dura, the walls of the arachnoid veins, around cranial nerves and around spinal roots.[12-14] From experimental work in which lymphatic channels were ligated it can be presumed that retrograde passage is possible. This creates another potential way of entry for the blast cells. Whether they afterwards take up a perivenous position is not clear.

Hematogenous spread: It was also proposed that leukemic cells gained access to the venous wall by passage through the endothelial lining. A careful pathologic study has elucidated the developments in meningeal leukemia and its gradual progression.[9] Initially leukemic cells became apparent in the walls of the superficial veins in the arachnoid. It was remarkable that the walls of the arteries were free. In a more advanced stage the leukemic infiltrate filled the trabeculae and encased the arteries. In the beginning only the superficial portion of the tissue was involved. The CSF space became gradually compressed. Malignant cells could egress from the trabeculae into the CSF as the process evolved. The deeper portions of the arachnoid along the vascular distribution in the brain parenchyma were infiltrated as a further step. Even in this advanced stage the infiltration stayed extraneural. It resulted in compression of vascular structures, cranial nerves and spinal roots. Ultimately the glia limitans was destructed. Only at that time invasion of the neural parenchyma proper could be seen.

Essentially the invasion of the dura was regarded as following the same basic pattern and distribution as in any connective tissue structure in the body.[15] This was largely concentrated along the venous channels. The infiltrates disrupted small capillaries at the undersurface of the dura, thus producing petechial hemorrhages. Through a repetitive process and subsequent fibrosis chronic subdural hematoma could develop.[16]

De novo

Malignant transformation of undifferentiated germinal elements with hematopoietic potential in the venous walls is theoretically possible.[17]

Additional facts

Factors which could influence the concept how leukemic cells enter the CNS are the following: A similarity in chromosomal abnormalities in the leukemic cells in bone marrow or blood and in the CSF has been noted.[18] This favors a

metastatic process, assuming that one circulating stem cell can form colonies. That the growth in the meninges is blood borne is also reflected in the fact, that lymphoma patients with leukemic transformation experienced involvement of the meninges, indistinguishable from ALL. Bone marrow involvement also predisposed for developing MenLy.

Harder to explain are the cases in which intracranial leukemia preceded systemic disease. Do these early lesions arise locally or are they metastatic? Immune defenses are known to be weaker in the CNS than elsewhere. In extracranial sites the growth may be retarded whereas the proliferation in the CNS can continue unimpeded and will give rise to earlier detection.

The development of primary malignant lymphoma of the CNS, although not the subject of this review, needs nevertheless also to be explained.

EVOLUTION OF MENINGEAL LEUKEMIA AND LYMPHOMA

During a certain time after the initial diagnosis a linear relationship exists between the survival time and the incidence of ML, whereafter the rate of appearance falls.[19,20] This suggests that factors operating at the time of diagnosis influence whether or not the brain is seeded. Contributive factors are: a high WBC count or a large tumor load, low platelet level, T-cell and B-cell leukemias and lymphomas, and monocytic leukemia. At the time of a systemic relapse the same factors are in action.

Proliferation rates of the leukemic cells in the CNS proved to be remarkably slow.[21,22] Incidental cases with a very long interval between remission and a CNS relapse, even up to 10 years underscore these observations.[23]

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4. CLINICAL MANIFESTATIONS OF CNS LEUKEMIA AND LYMPHOMA

CNS disease can be present at the time of the initial diagnosis of a hematopoietic malignancy, can occur as the first relapse or simultaneously with systemic relapse, and can evolve during active systemic disease. When CNS prophylaxis was not given to NHL patients, approximately one half of the CNS localizations became manifest during active disease, one fourth was present at initial diagnosis and the rest was equally divided between primary CNS relapses and combined systemic and CNS relapses.[1] The distribution of the appearance of CNS disease in leukemia has changed in conjunction with the applied systemic and prophylactic CNS treatment.

Tumor formation in CNS leukemia is not frequent anymore, due to current effective systemic therapy. Clinically documented intracerebral lymphoma is being reported with increasing frequency.[2,3] Dural lesions in NHL are frequently found at the base of the brain, sometimes with invasion of the cavernous sinus, but it can also be encountered over the convexities. The symptomatology of the tumor presentation in the brain as well as dural is completely dependent on the localization.

Diffuse leukemic infiltration of the neural parenchyma without ML is rare.[4,5] In secondary CNS lymphoma diffuse infiltration is also rare, but when it occurs it shows a propensity for a subependymal distribution. Confusion, deficits in recent memory and immediate recall are in line with such a periventricular localization.[6]

Hemorrhages in the course of leukostasis in the brain or together with leukemic infiltration in the dura or as a consequence of thrombocytopenia don't differ in their symptomatology from hemorrhages by other causes.[7,8]

So the description of symptoms and signs can be focused on ML and MenLy.[8,9] This diagnosis is suspected when the patient has signs and symptoms of structural lesions involving the neuraxis at more than one anatomic site. Typically the neurologic signs suggest more widespread dysfunction than do the patients complaints. The signs can be divided in three groups: there are those resulting from cranial nerve or spinal root involvement, those accounted for by the obliteration of the CSF pathways and those due to the irritation component of the meningeal infiltration. Preference of the disease for the basal meninges explains the frequent involvement of the cranial nerves. The VIIth, VIth, IIIrd and Vth nerve are most often affected in this order. The dysfunction can evolve gradually, but in some cases the motor deficit is nearly complete in one or two days.[10] All cranial nerves have been mentioned as having been involved in ML. Infiltration of the cranial nerves accounts for the greater part of these lesions. Hemorrhages and infarcts in the nerves explain probably part of the more acute presentation. The same holds true for the spinal roots, of which

the cauda equina is the most frequently involved.[11] This part of the manifestations has a localizing quality.

Another part of the symptomatology is due to infiltration of the arachnoid proper. As reaction to this process signs of meningeal irritation may be present: such as headache, nuchal rigidity and pain on straight leg raising. These signs are often mild. Besides this the leptomeningeal infiltration can cause obstruction of the CSF flow and it can hamper CSF resorption. As a consequence intracranial pressure will rise and hydrocephalus may develop. In this context the signs and symptoms are generalized: that is, headache, lethargy, confusion, vomiting and ataxia.[9] The literature concerning children with CNS leukemia mentioned convulsions and papilledema as presenting signs as well.[12] In our experience with adults this was nearly never the case. The earliest symptoms in adults were usually a vague headache, subtile mood changes and cranial nerve dysfunctions.

Focal brain dysfunction becomes evident only later in an advanced stage of meningeal disease, when the brain parenchyma gets infiltrated. An exception especially in children can be the hypothalamic-hypophyseal dysfunction, which can appear earlier during the disease course.[11] Infiltration with leukemic cells was the most frequent cause, either in the hypothalamic region, the hypophyseal stalk, the posterior hypophysis or the hypophyseal capsule.[13-15] Other cases were caused by thrombosis or infarction.[16] This relates to another possibility of CNS dysfunction, namely hypoperfusion encephalopathy. When the vessels are compressed by the arachnoidal infiltrate, vascular insufficiency and stasis may lead to a fluctuating symptomatology of a focal nature.

Essentially not much difference exists between the clinical presentation of CNS involvement in ALL, acute myelocytic leukemia (AML) and NHL. However one has to keep in mind that in NHL and AML epidural tumor formation in the spinal region is more common. Spinal root dysfuction and/or spinal cord compression will result depending on the level and the position of the lesion.[17,18]

Peripheral nerves have been reported to be invaded by leukemic and lymphoma cells in only a few cases.[10,19-22]

Besides the disease patterns that can be attributed directly to metastasis or extension of leukemia and lymphoma, there are several other factors during the disease course, which may cause nonmetastatic neurological problems. Complications of therapy will be dealt with later.

Abnormal coagulation parameters are frequently demonstrated in cancer patients. The lymphoma and leukemia patients are amply represented in this category.[23] Not only thrombotic but also hemorrhagic accidents may occur.[24]

Acute promyelocytic leukemia carries a marked risk for coagulopathies.[25] Disseminated intravascular coagulation (DIC) associated cerebrovascular accidents are a consequence of microthrombi of fibrin in the smaller vessels or due to occlusion of the venous sinuses.[26] Non bacterial thromboendocarditis (NBTE), another expression of coagulopathy contributes also to the cerebrovascular accidents.[23,27,28] Both DIC and NBTE may present as a diffuse encephalopathy with or without superimposed multifocal brain dysfunction.

Infections, bacterial, viral as well as fungal and parasitic, occur readily in these patients presenting as meningitis, encephalitis, abscesses, myelitis or myelopathy and as vasculitis. Opportunistic infections will virtually always be one of the items in the differential with CNS leukemia or lymphoma. Because of a disturbance in immune defenses, in part by the disease process itself, in part by the therapy, corticosteroids as well as cytotoxic therapeutic agents, patients get more susceptible to infections. In lymphoproliferative disease CNS infection is rarely the presenting manifestation of the disease.[29] The time lag from the onset of the immunosuppressed state to development of CNS infection was quite variable for different illnesses. The maximal risk of CNS infection in patients with acute leukemia occurs when their granulocyte counts have been less than $0.1 \times 10^9/l$ for several days. For NHL the median time lag was approximately 5 years and for patients receiving daily steroids 15 months. If this is compared with 2,5 years for M.Hodgkin, with 7 years for chronic lymphocytic leukemia and with 1 month for renal transplant patients, it becomes obvious that various factors contribute to the net state of immunosuppression. A defect in cell mediated immunity, a defective humoral immunity, a numerical or functional neutrophil defect, a splenic dysfunction and an interrupted integument are all attributive to the abnormalities in the host defenses.[29-31] Cell mediated immunity is disturbed in lymphoma and lymphocytic leukemia patients, after bone marrow or organ transplants and in patients on steroids. Severe neutropenia is mostly caused by cytotoxic chemotherapy. Depending on which defect prevails, certain infections become more common.

Infections in patients with a disturbance of cell mediated immunity were mainly caused by listeria monocytogenes, cryptococcus neoformans, toxoplasma gondii, aspergillus, varicella-zoster and papova virus.

The microorganism most commonly responsible for meningitis in patients with a normal WBC count was listeria monocytogenes. In patients with depressed WBC's Gram negative rods were virtually always the offenders.[32]

Patients with hypogammaglobulinemia or splenectomies don't regularly belong to the ALL, AML or NHL patient groups. Hence their special infections will not be commented upon in this review.

The organisms which caused CNS infections following neurosurgery and the placement of reservoirs or shunts belonged to the resident skin flora, such as staphylococcus epidermidis.[30]

Fungal agents initiating infections were cryptococcus neoformans, aspergillus and candida. The first causes meningitis and the other two cause brain abscesses. Through recrudescence of a latent toxoplasma infection disseminated disease can develop. The nervous system gets often involved in this disseminated process. The picture can vary between a more diffuse meningoencephalitis and the formation of abcesses.

Viral infections, such as herpes zoster and measles can take a more virulent or unusual course. Herpes zoster infection in these patients stays not restricted to the sensory ganglion cells, but can involve meninges and motor neurons. The spinal cord and brain are more diffusely affected.[33-35] A cerebral vasculitis is also one of the possibilities. Progressive multifocal leukoencephalopathy, a rare infection by a papova virus, has been particularly associated with the hematopoietic malignancies.

Signs and symptoms of all these infections, meningitis as well as encephalitis are mostly not very prominent. Fever and mental status alterations are frequently the only indications. This encephalopathy is virtually indistinguishable from a metabolic encephalopathy. Signs of meningeal irritation are often absent. Accompanying cerebral parenchymal and meningeal small vessel vasculitis may explain the severity of the encephalopathy.[32] When focal lesions or seizures develop, aspergillus and toxoplasma can be the causative agents.

In some cases malnutrition contributed to the development of Wernicke's encephalopathy.[36] The lesions in a pathology study indicated a chronic disease state with a preterminal exacerbation. This chronic form of the disease was marked by stupor with few or no ocular signs. This encephalopathy is caused by a vit. B1 deficiency.

Subacute combined degeneration of the spinal cord due to a lack of vit. B12 is rare in these patients. Paraparesis and decreased sensation for pain, vibration and position sense plus a mild peripheral polyneuropathy fulfilled the criteria for this disease in one patient.[37] In the same abstract degenerative spinal cord lesions of an undetermined cause were mentioned in 31% of patients dying from ALL. In myelopathy combined with polyneuropathy a pathogenic role has also been suggested for an abnormal immune response to microbial agents.[38] These disease states are clinically underdiagnosed during the end stage of the illness. The aetiology is probably diverse, such as deficiency states, viral infections and disturbances of immunologic processes.

Even rarer are the paraneoplastic effects in acute leukemia and NHL. Subacute motor neuronopathy has been seen in M.Hodgkin and NHL, for which a viral aetiology was hypothesized and radiation therapy could have contributed as well. This syndrome had a benign course compared to other lower motor neuron disease forms. The illness is characterized by a subacute progressive

painless often patchy asymmetrical lower motor neuron weakness involving legs usually more than arms, while sensory loss is absent or mild.[39-42]

A contrast image is formed by the subacute sensory neuropathy which has been associated with carcinoma, M.Hodgkin and NHL. Over a period of weeks the patient experiences a progressive loss of all sensory modalities in the extremities with relative preservation of motor power. While it is reported to carry a poor prognosis when associated with carcinoma, it was remarkable that it remitted during treatment for lymphoma.[43-45]

Polyneuropathies of the sensorimotor type with acute, subacute and chronic presentation or a remitting and relapsing course have also been associated with leukemia and lymphoma.[46] Their aetiology is not well clarified as yet and may include immunological mechanisms, toxic, metabolic, nutritional and vascular causes and viral infections.

Myoclonus, ataxia, dysarthria and nystagmus were demonstrated to be due to a loss of Purkinje cells in the cerebellum.[47-48] This disorder is mainly associated with small cell lung cancer and ovary cancer, but sporadic cases have been reported in M. Hodgkin and leukemia.[49] In the serum of some of the patients with carcinoma and paraneoplastic cerebellar disease antibodies against Purkinje cells have been found. CSF samples could also be positive. Their role in the pathogenesis of this syndrome has not been solved and the antigenic stimulus for these antibodies is not known.[50,51] It has been suggested that the paraneoplastic cerebellar cortical degeneration may result from a cross reaction of antibodies against lymphocytes with Purkinje cells, since they share immunologic markers.[52]

Polymyositis has been observed in acute leukemia.[53]

A certain degree of overlap may exist between the paraneoplastic syndromes. Quite often the paramalignant syndromes take a course independent from the underlying disease.

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5. DIAGNOSTIC PROCEDURES

CEREBROSPINAL FLUID

The examination of the CSF is essential to confirm a clinical diagnosis of ML or MenLy, to screen patients who are at risk for developing this complication, and to monitor the results of the treatment of established ML and MenLy.

Normal CSF

The lumbar CSF pressure ranges normally between 50 and 200 mm water.[1] The protein content of the CSF depends on the determination method used, but is lower in the ventricular than in the lumbar compartment. Reference values from the CSF laboratory of the Department of Neurology of the University of Groningen are lumbar 0.20-0.55 g/l and ventricular less than 0.10 g/l. Glucose values are dependent upon the blood level. The CSF/blood glucose ratio is 0.50-0.75.

The cell count has to be ≤4 cells /mm^3. The CSF cytology is composed of a few lymphocytes and monocytes and occasionally of cells from the ependyma, choroid plexus and the arachnoid. The ratio between monocytes and lymphocytes is 3:2. Polynuclear leucocytes don't belong to the normal picture.[2,3] Since often only a few cells are present in a CSF sample, they must be concentrated for cytological evaluation. Several techniques have been developed. These methods can be based on centrifugation or on sedimentation. Although cytocentrifugation has been considered to collect a great percentage of the cells present, it has the disadvantage that cells become often distorted by the centrifugal force.[3,4] The sedimentation technique was originally introduced by Sayk.[5] The cell loss was considerable because of cell absorption by the filter paper. Improvements of this method have been described with which the cell yield can reach 90%.[6,7] The controversy concerning the superiority of one method above another has not been solved as yet. On the basis of an historical development two different techniques were used in our hospital. The CSF laboratory performed the sedimentation technique and the hematological laboratory made use of a cytocentrifuge. In the beginning only the latter method was available. Later on the results of both methods could be compared. Cell recovery by the sedimentation technique proved to be adequate. Even from CSF samples with cell counts of 0-1 cells /mm^3 slides could be made on which enough cells were available for evaluation. Cell morphology is better preserved with the sedimentation technique. Quite often this method has given us an earlier positive result in cases with CNS relapse than the cytocentrifuge method. Although no prospective investigation was done to settle the controversy, it became clear that extensive experience of the laboratory technicians is essential

for obtaining good results, whatever method may be used. All preparations were stained with May-Grünwald-Giemsa.

Definition of CSF diagnosis of ML and MenLy

Mostly the CSF diagnosis is not difficult in a leukemia patient who is clinically symptomatic for meningeal disease if the CSF cell count is over 10 cells /mm^3 and cytology positive for blasts, although an infection or a reaction to intrathecal therapy has to be excluded. Since it is essential to diagnose meningeal involvement in an early or a presymptomatic phase, one has to rely on the correct interpretation of less explicit CSF findings. The difficulties are underlined by the wide range of criteria used to define ML. Any number of blast cells has been considered indicative as have cell counts of ≥10 mononuclear cells /mm^3 in the absence of infection.[8,9] Others have labeled a specimen positive if any definitely immature cell was observed or the cell count was ≥5/mm^3. This conclusion was based on the observation that if the cell count was 5 or more, 94% of these cells was abnormal. When infection and blood contamination were ruled out, meningeal infiltration could be disproved in less than 1%. Furthermore when the CSF cytology was positive, but the count was normal, leukemic infiltration was likely in 90% of the patients with ALL. In that study falsely positive slide results were never seen with counts of more than 10/mm^3, but this could very well occur when the cell count was normal and the percentage of immature cells was less than 10.[10] A normal cell count is no guarantee that there are no blast cells in the CSF. Nearly one third of samples with normal counts in leukemia patients with and without known ML have been reported to contain blast cells.[11] The percentage of leukemic cells in this category can be as high as 40.[10] On the other hand in case of a pleocytosis it is considered necessary that the blast cells are the predominant cell type, i.e. that they make up 40-60% of the cells.[12] This avoids falsely positive results caused by blastlike reactions during viral infections. Other pitfalls can be created by the contamination of the CSF from leukemic peripheral blood or from bone marrow.[10,13]

Based on the literature and on our own findings, which included sometimes very frequent CSF sampling in the same patient during a long period, several requirements were formulated. These depended on clinical signs and symptoms and on the number, the morphology, and more recently on immunologic typing of cells in the CSF.

The diagnosis ML on the basis of CSF examination required: the presence of leukemic cells in any number or a cell count of ≥5 cells /mm^3, that could not be explained by infection, a toxic reaction or otherwise, together with clinical signs of meningeal disease. In doubtful cases the use of immunologic typing proved to be helpful. The diagnosis MenLy was made in a similar fashion.

In a patient with appropriate clinical suspicion the absence of malignant cells in the CSF does not exclude the diagnosis of leptomeningeal seeding. Repeated CSF examinations can eventually lead to positive findings.[14] In cases without demonstrable malignant cells in the CSF a favorable reaction to i.vt. cytotoxic drugs added empirical prove for the diagnosis ML/MenLy.

Additional findings contributive to the diagnosis ML/MenLy

Other CSF findings

Although in overt ML/MenLy an elevated pressure can be measured during a lumbar puncture, the protein content of the CSF can be elevated and the CSF glucose can be reduced, these facts play no role in early presymptomatic diagnosis. A raised protein content and a reduced glucose level are in no way specific for ML/MenLy.

Monoclonal antibodies

Since typing of malignant cells with monoclonal antibodies has become available it has also been shown that this can be used to distinguish between normal reactive lymphocytes and lymphocytes or lymphoblasts from a leukemic lineage. Whenever doubts exist about the nature of certain cells in the CSF it can be helpful to investigate their markers.[15-17]

Biochemical markers

Whether biochemical markers have any early diagnostic potential for ML/MenLy has still to be settled. One possible useful marker is beta$_2$microglobulin ($ß_2$-m). This is a cell membrane component, closely associated with HLA antigens. It has been stated that the CSF $ß_2$-m level correlated with clinical evidence of meningeal involvement in leukemia and lymphoma patients.[18] Recently it was considered to be a sensitive marker for leptomeningeal infiltration by hematopoietic tumours and an effective monitor for the results of chemotherapy.[19] The reference values however have to be standardized for age.[20] Furthermore the ventricular level is approximately half the lumbar level. Not only is CSF $ß_2$-m elevated in the above mentioned category of patients. This occurs also in leptomeningeal carcinomatosis, and with epidural and cerebral metastasis of solid tumors, when they are in close proximity of the ventricle or subarachnoid space and even more so in meningitis and after cerebral radiation. Because of the unreliability to distinguish between viral infection and CNS leukemia other authors considered $ß_2$-m not an appropriate test for early detection of ML/MenLy.[21]

RADIOLOGICAL PROCEDURES

Computed tomography (CT)

Cranial CT has the greatest significance for intra-axial lesions. Leukemic tumors show regions of decreased attenuation with surrounding white matter edema. Lesions enhance with a rim pattern following contrast administration. The lymphomatous infiltrations are mostly isodense or slightly hyperdense on precontrast scans with homogenous enhancement after contrast.[22] In the acute phase leukemic or lymphomatous masses must be differentiated from infections, hemorrhages and reaction to therapy such as acute necrotizing leucoencephalopathy. Sometimes CT will detect the more chronic sequelae of radiotherapy and chemotherapy, for instance dilatation of sulci and the ventricular system or leucoencephalopathy with calcification.

Leptomeningeal infiltration by hematopoietic tumor is difficult to detect with CT.[23] Findings such as: obliterations of the cisterns and sulci, hydrocephalus with transependymal edema and contrast enhancement of cisterns, sulci and ventricular lining are considered to be specific.[24] However, cytological documentation tends to precede the CT detection. Often the clinical signs and symptoms of ML/MenLy are already abundant before the CT will show any abnormalities. Enhancement in ML/MenLy is much less than in meningeal carcinomatosis. The reason for the poor visualization of ML/MenLy is not clear. Although the use of corticosteroids as one of the therapeutical agents in these patients may play a role, it certainly does not account for the inability to demonstrate enhancement of the meninges in most patients. Serial CT scans are relatively more sensitive. They can reveal the asynchronous enlargement or obliteration of some spaces characteristic of ML/MenLy, in contrast to the more simultaneous and proportional enlargement of ventricles and subarachnoid space after radiation or steroids.

Dural infiltrations are rare. They are often focal and may be misinterpreted as artifacts, because of the immediate proximity to bone.[25]

Myelography and CT-Myelography

In case of epidural compression by leukemia or lymphoma the aspect of the spine on plain X-ray studies is frequently normal.[26] The deposits can best be visualized by myelography and CT-myelography. In the future magnetic resonance imaging (MRI) will possibly replace part of these procedures.

Leptomeningeal infiltration will show as parallel longitudinal striations due to thickened nerve roots in the cauda equina, or takes the aspect of multiple nodular filling defects along the nerve roots of the cauda equina. Bizarre irregular filling defects with varying degree of blocks may be seen.[27]

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6. CNS PROPHYLAXIS IN ALL, AML AND NHL

In the nineteensixties the increasing incidence of ML in children with ALL was recognized. Prophylactic CNS therapy was then tried. The purpose was to eradicate the malignant cells, which had metastasized to the meninges. These cells were located in a "sanctuary", where they were not adequately exposed to systemic chemotherapy. The unimpeded proliferation of the malignant cells in the meninges led to significant morbidity. This could also form a potential source of systemic relapse.

The first effective CNS prophylaxis was reported from St. Jude Children's Research Hospital. Cranial radiotherapy with 2400 rad and simultaneously five doses intrathecal (i.t.) MTX 12 mg/m^2 given early in remission reduced the incidence of ML to $\pm$10%.[1] This regimen became the standard for comparison with results of other preventive therapies. Craniospinal radiotherapy (2400 rad) was equally effective but myelotoxic.[2]

The combination of cranial radiotherapy and i.t. MTX was associated with a considerable risk of neurotoxicity. (See chapter 1; 8) Several regimens were designed to prevent these side effects. A reduction of the cranial or craniospinal radiation dose to 1800 rad gave similar results as the St. Jude studies.[3] Cranial radiotherapy alone was insufficient in preventing primary CNS relapses.

On the other hand a relative short course of lumbar i.t. injections with MTX at the end of the induction phase was also unsuccesful.[4] This could be due to several factors. First, the reliability of the distribution of MTX introduced into the lumbar sac is questionable. Because of epidural leakage therapeutic levels of MTX can not be guaranteed above the foramen magnum.[5] Secondly, primary CNS relapses occurred at a fairly constant monthly rate during the first two years after remission.[6] This could be explained by the slow proliferation kinetics of leukemic cells in the CSF.[7] So a long-term eradication schedule is probably required. Regimens which took these factors into account had good results.[8-11]

A trial in children with ALL compared the results after i.t. multidrug therapy with the standard regimen. Prophylaxis started at induction or at complete remission (CR) and was maintained during 1 or 3 years. Patients received MTX 15 mg/m^2, hydrocortison (HC) 15 mg/m^2, and cytosine arabinoside (AraC) 30 mg/m^2. Primary CNS relapses were equally prevented, but infections were a serious complication when CNS prophylaxis was given early in induction.[8]

Trials of Memorial Sloan Kettering Cancer Center concerned children as well as adults. The dose of MTX was much lower. In the L-2 protocol CNS prophylaxis for children and adults differed. Children received 6.25 mg/m^2 MTX for three times during induction. Maintenance consisted of MTX twice weekly every 2 months for 3 years. Adults received only five to seven i.t. doses of MTX during the first two months of therapy. The results of the L-2 protocol were better in children than in adults.[9-10]

The L-10 and L-10M protocols were more intensive. CNS prophylaxis was administered twice weekly, three times during induction, two times during consolidation and every 2 months during a maintenance period of 3 years. Patients with initial WBC's over $20x10^9/l$ had an Ommaya reservoir inserted after CR had been achieved. The CNS prophylaxis was then administered through the reservoir. Adults received only MTX, whereas in children this was alternated with AraC. Primary CNS relapses were equally well prevented in children and adults. Their primary CNS relapse rate was 1.8 and 3.3%, respectively.[10-12]

Similar results were obtained in adults with ALL who received i.t. MTX, 12 mg/m^2, three times during induction and monthly during 2-3 years of maintenance treatment.[11] In another small study CNS prophylaxis consisted of i.t. induction therapy followed by i.vt. treatment. The total duration was less than four months. The primary CNS relapse rate was not as good, namely 16.6%.[13]

Generally CNS prophylaxis by chemotherapy alone can be effective, provided that it is administered long-term. The duration of this maintenance period has not been established as yet. It is also not decided when CNS prophylaxis should begin, at diagnosis, during induction or at CR.

The greater part of the discussions has concerned children with ALL. Gradually the need for CNS prophylaxis in adults with ALL became evident. The work of Price showed that the meninges were as much at risk in AML as in ALL.[14] However, the poorer prognosis of patients with AML has discouraged some authors to use CNS prophylaxis.[15,16] Other studies reached the conclusion that preventive CNS therapy in AML was justified for children and also for adults.[17-22] The best method to be used was even less clear than for ALL. The controversies about the need for CNS prophylaxis in NHL are numerous. It appears warranted in NHL with a high grade malignant histology.[23-29]

Most of these results were not known at the time our own CNS prophylaxis regimen was designed. Preference was given to a schedule that relied on i.vt. CNS prophylaxis, maintained during 6 months. The Ommaya reservoir was inserted in ALL and AML patients after achieving CR. In T-cell and B-cell ALL cases this procedure was performed as soon as circulating blasts had disappeared by systemic therapy. Patients with a WBC count over $100x10^9/l$ received the reservoir as soon as possible. CNS prophylaxis was originally given to all patients with AML, but later this was restricted to M4 and M5 subtypes. Patients with high grade malignant NHL had their reservoirs implanted when the response to systemic chemotherapy was favorable, mostly after 3 to 4 weeks. In ALL and NHL prophylaxis consisted of 15 mg MTX. A preservative free solution was used. AML patients were treated with 100 mg AraC dissolved in sterile isotonic saline. These drugs were administered every

4 weeks for six times. When the patient experienced a systemic relapse the CNS prophylaxis was repeated.

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7. TREATMENT OF MENINGEAL LEUKEMIA AND LYMPHOMA

Effective CNS therapy is needed for those patients, who present with ML/MenLy or who develop active meningeal disease despite CNS prophylaxis. The choice of therapeutic modalities is nearly the same as outlined for CNS prophylaxis.

Although radiotherapy of the entire neuraxis at a dose of 2000-2500 rad was effective in obtaining CNS remission it also caused severe myelosuppression. In this way it proved to be prohibitive.[1]

Most authors agree on the use of i.t. or i.vt. therapy with MTX or AraC to clear the CSF of blast cells. The length of such a remission is short (3-4 months). Maintenance i.t. therapy given at certain intervals prolonged this remission duration till 8 months.[2] The limited response obtained by chemotherapy may be explained by arachnoiditis and fibrosis causing interference with the free flow of CSF between the lumbar dural sac, the cranial subarachnoid space and the ventricles. Furthermore, patients with ML/MenLy can have dense malignant infiltrates that can obstruct the CSF flow. An Ommaya reservoir bypasses these obstacles to a great extent and circumvents the need for frequent spinal taps. Intraventricular chemotherapy is significantly more effective against CNS leukemia than the same therapy given by lumbar puncture. Patients with recurrent ML despite maintenance MTX injections into the lumbar CSF could be reinduced into remission with i.vt. MTX. The length of this remission was greater than the previous one, induced by the lumbar route.[3-5]

Once a CNS remission was established, consolidation by craniospinal radiotherapy (cranial 2500 rad, spinal 1000 rad) resulted in prolongation of the CNS remission duration of patients, who were treated for a first ML episode. This was not succesful in second or subsequent meningeal relapses. The toxicity was acceptable with a spinal dose of 1000 rad. Cranial radiation alone was insufficient.[6] Control of established ML has been difficult to achieve with regimens of cranial or craniospinal radiotherapy known to be effective in prophylactic treatment. So higher doses were advocated for isolated meningeal relapses despite prior prophylaxis. After initial clearance of CSF cytology by i.t. MTX, neuraxis radiation with 3000 rad to the cranial field and 1800 to the spinal one, prevented further ML episodes in these patients. The total radiation dose was high and significant neuropsychological alterations have been detected, although the quality of life of the survivors was described as acceptable.[7]

Another approach consisted of a combination of i.t. and i.vt. treatment and low dose radiation. CNS remission was induced by intralumbar MTX alternated with AraC. This was followed by the placement of an Ommaya reservoir. Subsequently the neuraxis was radiated with 600-900 rad. The chemotherapy was then continued for 3 years via the reservoir or alternatingly intralumbar and intraventricular.[8]

MTX has been the first drug of choice. Later studies added AraC and sometimes HC.[2] The optimum doses, schedules and the simultaneous or sequential use of these multiple agents are still to be determined. One of the newer drugs, which has been used for leukemia and NHL is mitoxantrone. Incidentally it has been tried in resistant ML with reasonable good reactions.[9,10] It can be argued that in concordance with systemic therapy in ALL and NHL the i.t. or i.vt. use of MTX is favored, while in AML AraC is preferred. The slow proliferation of leukemic cells in the CSF requires a therapeutic drug level during several days.[11,12] MTX meets this requirement. AraC however is rapidly metabolized. The addition of i.t. HC may reduce the incidence of chemical arachnoiditis, but the preparation itself is not free of a preservative, which may be toxic to the CNS.[13] Also HC has been shown to reduce the uptake of MTX by leukemic cells.[14]

An alternative was introduced by Bleyer et al.[12] Since neurotoxicity of MTX is associated with the total amount of MTX administered and with elevated drug concentrations in the CNS, they devised a regimen based on frequent low dose courses of MTX. The so-called "concentration x time" (CxT) regimen was given via an Ommaya reservoir. Six doses of 1 mg every 12 hours could be compared with the conventional single injections of 12 mg/m^2 . Both regimens were given in the induction phase and continued during 6 weeks of consolidation and 2 years of maintenance. The effectiveness for the rate of remission induction, the number of relapses and the remission durations were comparable. This regimen is theoretically attractive but it requires frequent visits to the clinic or hospitalization.

High dose MTX intravenous (i.v.) achieved MTX concentrations in the CSF of children with ML which were sufficient to obtain complete CNS remissions in 80% and partial remissions in the others.[15]

In adults treated with an intensive i.vt. triple drug schedule followed by cranial radiation (3000 rad) CNS remissions lasted longer when the meningeal disease episodes were asymptomatic. AML patients did better than ALL patients. Rapid attainment of meningeal remission was favourable as was early inital bone marrow (BM) remission. A long duration of the first BM remission was also a factor associated with a long duration of meningeal remission. The beneficial effect of radiotherapy was not statistically significant, but a certain trend in that direction was present.[16]

The significance of a first isolated primary CNS relapse is probably different from a CNS relapse occurring simultaneously or after recurrent disease. Patients in the later group carry a worse prognosis. Their risk for a BM relapse is higher.[8]

ML and MenLy in our patients were primarily treated by i.vt. chemotherapy. In ALL and NHL patients MTX was administered and in AML patients AraC was given. When MTX failed to induce a CNS remission, it was alternated with or it

was substituted by AraC. AraC was also used when the MTX concentrations in the CSF indicated that the patient metabolized the MTX rather slowly. After clearing the CSF of blast cells patients received a consolidation course of four weekly and two biweekly i.vt. injections. Maintenance was given every four weeks for six times. A meningeal relapse formed an indication to start reinduction systemic therapy.

In case of additional intraparenchymal CNS disease radiotherapy was given to the area concerned. Radiation was occasionally needed when in one of the subsequent ML/MenLy relapses reinduction by i.vt. chemotherapy failed.

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8. NEUROTOXICITY OF CNS THERAPY

Since 1970 the complications of ML treatment and CNS prophylaxis have been described in numerous articles. Information is derived from single case observations, retrospective analysis of patient data, prospective studies, neuropsychological test results, radiology studies and autopsy material. The greatest part of the reports concerned children. The sequelae of cranial and spinal radiation and i.t., i.vt. and i.v. chemotherapy will be reviewed briefly, although they are not equally relevant to our own treatment schedules. However, they are essental for deciding which method one prefers. The neurotoxicity signs may be classified into those occurring within hours to days after initiation of CNS therapy (acute), those beginning days to weeks later (subacute) and those not noted for several months to years (delayed).[1] In general the delayed toxicities are more serious and usually irreversible, and the acute and subacute forms are relatively benign or transient.

CNS RADIATION

The total dose in cases of leukemia and lymphoma is relatively low (±2400 rad).

Acute neurotoxicity

Conventional radiation is rarely associated with adverse reactions unless a high intracranial pressure already exists.

Subacute neurotoxicity

A subacute reaction is common even when the brain is radiated with a dose as low as 1800 rad. This occurs especially in the younger patients. The syndrome is characterized by somnolence, apathy, irritability, nausea and temporary exacerbation of preexcisting focal deficits.[2] The course is benign, but it remains to be established that this is not indicative of an increased risk of latent encephalopathy.[3] At the spinal level the equivalent is Lhermitte's sign. Both manifestations are thought to be due to a transient demyelination.

Delayed neurotoxicity

The radiation dosage required to produce atrophic changes may vary depending on the age of the patient (the infant brain presumably more susceptible), the presence of hypertensive or arteriosclerotic cerebrovascular disease, and damage to the blood-brain barrier by tumor. Since cranial radiation in leukemia and lymphoma is nowadays seldom given without chemotherapy

one has to depend on findings from the early CT era to define the degree of atrophy. Dilatation of the ventricles and widening of the sulci have been observed after 2400 rad.[4]

INTRATHECAL AND INTRAVENTRICULAR CHEMOTHERAPY

Acute neurotoxicity

MTX (max. 15 mg) and AraC (max. 100 mg) are the most commonly used chemotherapeutics for injection in the subarachnoid space or the cerebral ventricles.

Chemical meningitis is the most often encountered side effect following MTX injection. After AraC administration this has occurred less frequently.[5] It develops within 4-12 hours and is characterized by back or neck pain, nuchal rigidity, headache, fever, nausea, dizziness and occasionally vomiting. In most patients symptoms are not severe and decline in one or two days. The frequency is very variable and seems to be influenced by several factors. The presence of overt ML, the dosage, the administration schedule and pharmacokinetics (age dependent) are all contributive. Preservatives, an unphysiological pH and osmolarity of the preparation have also been indicated as possible offenders but their impact seems small.[6-8] The accompanying CSF abnormalities were an elevated protein content and a pleocytosis.[9] In general the course of the arachnoiditis is subclinical.

Subacute neurotoxicity

This type of toxicity appears related to high MTX levels in the CSF and prolonged exposition of the neural parenchyma to MTX.[10] The factors mentioned in the preceding paragraph are also causal for the subacute manifestations. In case of inadequate spinal CSF circulation a myelopathy may develop after i.t. drug administration.[11] An encephalopathy can result from i.vt. as well as from i.t. injections. Delayed CSF flow from the ventricles, frequently repeated MTX injections and diminished MTX elimination may play a role. The symptoms are generally reversible after the drug is discontinued or the dosage is reduced.[12]

Delayed neurotoxicity

Patients whose CNS prophylaxis was limited to i.t. MTX, did not show neurologic or cognitive abnormalities and had normal CT scans.[13,14]

HIGH DOSE INTRAVENOUS CHEMOTHERAPY

High dose MTX may cause a metabolic encephalopathy with confusion somnolence and seizures during or shortly after i.v. administration.[15] The metabolic aetiology has probably several components such as a deficiency of neurotransmitters, the production of toxic substances and inefficient removal of metabolic waste products.[16] The interruption of DNA production affects the myelin synthesis. Repeated cycles as used for osteogenic sarcoma can induce a leukoencephalopathy, detectable on CT as white matter hypodensity. The white matter anterior to the frontal horns is the most susceptible.[17]

AraC in high doses i.v. is especially toxic for the cerebellum, where Purkinje cells are the most vulnerable. Reversibility is often limited. A leukoencephalopathy is rare.[18-21]

CNS RADIATION AND I.T. OR I.VT. CHEMOTHERAPY

When both modalities are employed at the same time, an acute encephalopathy may develop. Patients with a large intracranial tumor load were more at risk.[22,23]

The late effects of radiation and MTX are of more concern. The cerebral white matter was most frequently involved. The leukoencephalopathy can be detected on CT scans in an early phase as decreased attenuation and in a later stage as cerebral atrophy with calcifications.[4,24] Early changes may be transient.[25] The regular schedule of five to six i.t. injections was already enough for the development of a leukoencephalopathy, when cranial radiotherapy had preceded these injections. The risk increased when the brain was continuously exposed to MTX over a prolonged period. Pathology studies of severe cases revealed a diffuse reactive astrocytosis with multiple noninflammatory necrotic foci, often containing varying amounts of mineralized cellular debris. Demyelination and glial cell loss were present as was axonal damage.[26,27]

The clinical picture was consistent with this white matter disease and eventually led to severe dementia and decerebrate posture. The possibility for long term sequelae of this standard CNS prophylaxis is greater in children, the younger the patient at the time of radiation.[28,29] Effects can be subtle.[30] Deficits were noted in the mean intelligence score and in memory and motor skill tasks.[31-33] It is conceivable that patients with overt meningeal infiltration who are exposed to MTX over a prolonged period, are at greater risk.[34] In addition a microangiopathy may develop in patients younger than 10 years. Lesions are mainly found in the grey matter of the putamen and the cortex around the depth of the sulci.[35]

The effect of AraC in this context is probably much smaller, since this is seldom mentioned.

MRI has been shown to be more sensitive than CT for identifying leukoencephalopathy.[36]

CNS RADIATION AND I.V. CHEMOTHERAPY

When the blood-brain barrier is damaged by radiation, i.v. chemotherapy adds to the potential neurotoxicity.[37,38]

One of the late effects of CNS radiation can be the induction of second malignant tumors such as meningioma, sarcoma and glioma.[39]

In conclusion it can be stated that the use of more than one treatment modality enhances the risk for neurotoxicity and that the disturbances caused by cranial radiation even at a relatively low dose hamper a subsequent use of chemotherapy.

THE OMMAYA RESERVOIR

This implantable device was introduced in 1963 by Ommaya for the treatment of fungal meningitis.[40] The indications for its use increased steadily and include now besides instillation of drugs for difficult to treat meningeal infections, drug level monitoring and the treatment of a variety of neoplastic conditions in the CNS, both prophylaxis and therapy. It has also been used for the drainage of cystic tumors, ventricular drainage and the delivery of analgesics in cancer patients.[41-44] Controversy still exists about some of these indications. Quite often this resulted from complications met by the authors, such as obstruction of the device, infection, and focal or diffuse leukoencephalopathy.[45-49]

The patient is the one who benefits of this form of access to the CSF in the first place. Spinal taps certainly if they have to be repeated often, cause considerable discomfort. In contrast, puncturing of the reservoir with a fine butterfly needle is nearly painless. Another advantage is that drug administration via the ventricular route has been shown to reach higher and more predictable CSF drug levels than when given by lumbar puncture. Frequent sampling of the CSF is made possible and helps to detect CNS relapses of leukemia and lymphoma early.

As a disadvantage the risk of infection has been mentioned. Meticulous preparation of the skin over the reservoir prior to sampling and injection will diminish this risk considerably. Problems related to insertion can be prevented by neurosurgical expertise.[44,50,51] The most common reason of malfunction is plugging of the catheter. This can be brought on by the CSF composition (elevated protein), by blockage by the choroid plexus, or by migration of the catheter tip.

From a study that compared i.vt. with i.t. chemotherapy in ML it was concluded that the first was significantly more effective.[52] The benefit-risk ratio is of special concern with the prophylactic use of the reservoir.

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9. CONCLUSION

CNS prophylaxis in ALL, certain forms of AML and high grade malignant NHL was considered necessary.

Out of concern for the neurotoxicity of the combination of early prophylactic cranial radiation and subsequent chemotherapy an alternate method was investigated. This method consisted of administration of chemotherapeutic drugs into the CSF as the only modality for CNS prophylaxis. Herefore the i.vt route with the use of an Ommaya reservoir was preferred since it offers easy entrance to the CSF. This facilitates frequent diagnostic CSF sampling and it eases drug delivery into the CSF along a physiological path.

In cases of meningeal involvement the i.vt. instillation of cytoreductive drugs is an accepted method of treatment. By devising an extensive CNS treatment regimen via the Ommaya reservoir prevention of or delay in the use of neuraxis radiotherapy was sought.

The results of the i.vt. administration of cytoreductive drugs in patients with ALL, AML and high grade malignant NHL, especially when used for CNS prophylaxis were evaluated. Furthermore the effects on meningeal involvement in these diseases were studied. Special attention was paid to side effects and complications of this treatment modality.

The purpose was to answer the following questions concerning

CNS prophylaxis:

1. Is CNS prophylaxis with i.vt. chemotherapy at least as good as the "generally accepted standard" method* ?
2. Can this form of CNS prophylaxis repeatedly be applied?
3. Is this treatment modality acceptable as preventive measure in relation to its neurotoxicity and its complication rate?

Treatment of ML an MenLy:

4. How effective is i.vt. chemoterapy for meningeal involvement?

Both categories:

5. Is this method convenient for the patient?
6. Are there any problems attached to this treatment modality which need to be addressed in the future?

*Cranial radiation (2400 rad) and i.t. MTX (5-6 times in 2,5-3 weeks)

CHAPTER 2

ACUTE LYMPHOBLASTIC LEUKEMIA IN ADULTS: RESULTS OF INTRAVENTRICULAR MAINTENANCE CHEMOTHERAPY FOR CENTRAL NERVOUS SYSTEM PROPHYLAXIS AND TREATMENT

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Abstract *The results of intraventricular (i.vt.) chemotherapy in 36 cases of adult acute lymphoblastic leukemia (ALL) were analyzed to define a useful and reliable form of central nervous system (CNS) prophylaxis. Patients received methotrexate (MTX) via an Ommaya reservoir six times every 4 weeks. This was repeated when bone marrow relapse occurred. Intraventricular maintenance CNS prophylaxis during half a year appeared adequate, since primary CNS relapses were seen in only two patients (5.6%). These patients had failed to follow the prophylaxis schedule. The procedure was implemented and repeated relatively easily and did not lead to neurotoxic problems.*

The i.vt. route was also satisfactory for the treatment of initial and recurrent episodes of meningeal leukemia (ML). The therapy reduced morbidity caused by ML to a minimum.

INTRODUCTION

Improvements in systemic chemotherapy have gradually prolonged survival time in adults with acute lymphoblastic leukemia (ALL). Meningeal leukemia (ML) has then become a problem in adults just as in children. Without central nervous system (CNS) prophylaxis to protect the meninges around the entire neuraxis, this complication occurs in up to 60%.[1-5] The basis of the pre-symptomatic treatment has been cranial radiation of 24 Gy in combination with five to six intrathecal (i.t.) injections of methotrexate (MTX). Following treatment the incidence of primary CNS relapse in children varied between 5 and 15%.[6-10] The results in adults were very similar.[11-13] However, this combination can cause a leuko-encephalopathy, especially in the developing brain, which

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results in neurological symptoms and a lower performance in neuropsychological testing.[14,15] This has led to the search for less toxic alternatives. It has been shown that 18 Gy cranial radiation is as effective as 24 Gy.[7,16] Another possibility is to use i.t. drugs alone, administered directly in the lumbar subarachnoid space or in the cerebral ventricles through an Ommaya reservoir.[6,10,17-20] The latter has several advantages: it avoids disturbance of the blood-brain barrier by radiotherapy; it offers a predictable distribution of drugs along physiological pathways; and it easily allows examination of the cerebrospinal fluid (CSF). In this study we report on the use of intraventricular (i.vt.) chemotherapy for CNS prophylaxis and treatment of ML. The efficacy and toxicity of this approach were studied in 45 successive adult ALL patients.

PATIENTS AND METHODS

Prophylaxis

Thirty-six adult ALL patients received i.vt. chemotherapy for CNS prophylaxis from July 1976 until July 1986. An Ommaya reservoir was inserted in most cases immediately after achieving complete remission (CR). In T-cell and B-cell ALL patients this was done as soon as circulating blasts had disappeared by systemic therapy. Patients with a mediastinal mass and circulating lymphoblasts of T-cell phenotype were excluded from this evaluation.

The implantation was preceded by a spinal tap to exclude asymptomatic ML. CNS prophylaxis consisted of six injections of 15 mg MTX, every 4 weeks. When a bone marrow (BM) relapse occurred a new CNS prophylaxis course was initiated. In the case of a CNS relapse i.vt. treatment was repeated together with systemic reinduction.

Treatment

Fourteen patients with ML were treated via the i.vt. route. ML was diagnosed when any number of blast cells was seen in the CSF or in case of pleiocytosis of 5 or more cells/mm^3, which could not be explained by infection or other complications. Five patients had received CNS prophylaxis. The other nine patients belonged to three categories: asymptomatic ML was present in five patients at initial diagnosis; overt ML appeared at the end of induction in two cases; in the other two ML occurred simultaneously with the first systemic relapse. One of the latter was referred, the other had refused standard prophylaxis. Two patients in the first category never achieved BM remission.

For ML, i.vt. MTX was given every 4 days until clearance of the CSF. The MTX dose was adjusted according to the MTX levels in the CSF. When the response was inadequate, MTX was alternated with 100 mg cytosine arabinoside (AraC), or it was substituted by AraC. After obtaining CNS remission, CNS consolidation was established with four weekly and two biweekly injections. Thereafter CNS maintenance was given six times every 4 weeks.

Systemic induction chemotherapy consisted of daily prednisolone (P) for 6 weeks and weekly vincristin (V) which was combined with doxorubicin (A) during the last 3-4 weeks. CR was followed by consolidation with asparaginase. Patients failing to achieve CR were given an AML-like course with AraC, 6-thioguanine and A. Maintenance therapy with V, P, 6-mercaptopurine and MTX was continued for 3 years, or until relapse of ALL. Four patients received a bone marrow transplantation in first remission.

The log-rank test was used for statistical analysis of survival data.

RESULTS

Patient data and risk factors for the development of ML are summarized in Table 1. Based on the literature a white blood cell (WBC) count over 25 x 10^9/l, platelets lower than 20 x 10^9/l and an elevated serum lactic dehydrogenase (LDH) were considered to be risk factors for ML.[5]

Table 1. Patient characteristics

	Prophylaxis		ML
Number	36		9
Sex m/f	22/14		5/4
Age (years)	14-62		16-73
median	22		52
Type:			
common-ALL	24	(4)	6
T-ALL	6		1
B-ALL	-		2
nonB,nonT-ALL	6	(1)	-
Initial WBC x 10^9/l			
<25	27	(3)	3
>25	9	(2)	6
Initial platelets x 10^9/l			
<20	6		2
>20	30	(5)	7
Serum LDH U/l			
<600	18	(2)	4
>600	18	(3)	5

Number of patients developing ML in parentheses

Efficacy of CNS prophylaxis

The overall results are summarized in Table 2. CR was achieved in all 36 patients, 13 of whom remained free of disease with a median follow-up of 33+ months. In this category two patients died of unrelated causes (chondrosarcoma, suicide). Patients who relapsed did so within 1-79 months (median 9 months). Five patients developed ML: three simultaneously with BM relapse at 3, 11 and 71 months. In two patients who had not received optimal

Table 2. Results of CNS prophylaxis and treatment

	Prophylaxis +	Prophylaxis + ML +	Prophylaxis - ML +
Number	36	5	9
1st remission duration	15 (1-104+)	10 (1-56)	7 (1-8)
Survival	40 (3-118+)	18 (13+-72)	10 (4-23)
Survival from Dx ML	-	11 (1-26)	5 (0-22)
CNS remission duration	-	4 (4-7)	4 (1-16)

Values in months, range in parentheses
Dx: diagnosis

prophylaxis ML terminated CR (5.6%). Insertion of the reservoir was delayed in one case due to infection, while in the other the prophylaxis was disrupted because the draintip needed replacement.

Efficacy of ML treatment

Results of CNS treatment in nine cases without prophylaxis and in five cases with prior prophylaxis are given in Table 2. Of the 14 patients three were not evaluable: one died of systemic disease shortly after placement of the reservoir; another preferred radiation treatment. In the third patient, who relapsed in BM and CNS after 6 years, the drain was not functioning well and craniospinal radiation was given before malfunctioning of the device could be corrected. The patient, however, died of systemic disease. CNS remission could be obtained in all evaluable patients. The median duration of the first CNS remission was 4 months, it was shorter in patients with overt ML (2 months) than in asymptomatic patients (6 months). Patients with CNS relapses had a median survival of 17 months (range 4-72). In four patients CNS remission continued till death, and one was still in remission (6+ months), when the study was closed. The median survival from diagnosis of ML was 7 months (range 0-26). The CNS prophylaxis group had better results (see Table 2).

Final outcome and comparison between subgroups are given in Table 3.

Table 3. Comparison of remission duration and survival between different subgroups

		Median Value (months)	P value
Survival	P+/P-	40 /10	<0.005
	ML-/ML+	58 /17	<0.025
	P+ML+/P-ML+	18 /10	<0.10
	P+ML+/P+ML-	18 /58	<0.50
Remission duration	P+/P-	15 /7	<0.05
	P+ML+/P-ML+	10 /7	<0.30
	P+ML+/P+ML-	10 /24	<0.40
Survival from Dx ML	P+/P-	11 /5	<0.60

P = prophylaxis, ML = meningeal leukemia, +/- = present/absent

Complications

Two types of technical problems were encountered. Drain occlusion necessitated renewal in two patients after 1 and 6 years. In another patient the drain-tip wandered from the ventricle to a subependymal position; this required repositioning.

Patients received cotrimoxazol for 3 days as pre- and postoperative therapy when the reservoir was inserted. Bacterial meningitis was diagnosed when bacteria could be identified in the CSF. Meningitis followed reservoir handling in three cases, once postoperatively and in two instances after puncturing the reservoir. The infections were caused by bacteria from the permanent skin flora. Symptoms and signs were always mild without cranial nerve involvement. A week long course of intravenous (i.v.) and i.vt. antibiotics (cefradine or cefuroxim) cured the meningitis without the necessity of removing the reservoir.

One ML patient experienced a mild reversible MTX encephalopathy.

DISCUSSION

Although prophylactic therapy has greatly diminished the occurrence of ML, which method is the most effective and the least neurotoxic is still under discussion.[21] Even studies using the same method (cranial radiation with ± 5 i.t. MTX injections) have considerable variations in effectiveness. The rate of primary CNS relapses in children varied between 1.3 and 15%.[6-10,17,22] The incidence in adults was 0-10.7%.[11-13] The inconsistency in outcome was more pronounced when lumbar i.t. MTX alone was used. The incidence of primary CNS relapses in children was as low as 5.5-6.9% or as high as 18.5-44%.[6,7,10,17,19] The better outcome was perhaps due to a longer period of prophylaxis (1-3 years). At the Memorial Hospital in New York the primary CNS relapse rate of adults was 11.1% on the L2 protocol and 2.8% on the L10-L10M protocol.[19,20] In another study the rate was 4.3%.[13] The lower incidences corresponded with i.t. treatment maintained during 2-3 years, and with the use of the i.vt. route in patients with an initial WBC count over 20 x 10^9/l in the L10-L10M study. Systemic chemotherapy was also more intensive in the latter. It is of interest to note that adults on the L2 protocol, in contrast to children, did not receive maintenance i.t. MTX.[23]

In our study only two cases of ML in the prophylaxis group were primary CNS relapses (5.6%). This is comparable with the results in other studies, since the prophylaxis in these two patients was not optimal.

The choice between the different CNS prophylaxis methods is determined not only by the effectiveness. Long-term side-effects, interference with other treatment modalities and ease of application must also be considered. In adults the impact of an isolated CNS relapse is probably different from the same event in children who experience less BM relapses and have longer remission durations.[24] Since the meninges are at risk with every new episode of leukemia, the CNS prophylaxis in adults must be designed in such a way that it can be repeated easily. Leukemic cells can remain dormant in the CNS.[25] This requires long periods of treatment, but the exact length has not been determined. A reservoir facilitates extended treatment and reliable distribution of drugs in the subarachnoid space.[26] Also it enables frequent CSF examinations essential for diagnosing still asymptomatic ML, and drug level monitoring. Lumbar i.t. injections of toxic drugs can cause local inflammation and fibrotic reactions, which make spinal taps gradually more difficult to perform and drug distribution unreliable. These drawbacks of i.t. injections are avoided by the i.vt. approach. Following i.vt. injections, chemical arachnoiditis was rare. In one elderly patient with symptomatic ML a mild but reversible MTX encephalopathy was seen. The metabolic rate in older patients is often lower.[27] Therefore in older patients and in patients with blockage of the CSF pathways, we now start with a lower dose of MTX and the CSF drug levels are determined more frequently.

The question remains why the Ommaya reservoir has not been used more often for prophylactic purposes since the i.vt. administration of drugs has been the accepted therapeutic modality for ML, meningitis carcinomatosa and fungal meningitis.[28-31] One important factor could be that CNS prophylaxis originates from childhood series. Adults are certainly more verbal, complaining about the unpleasant repeated spinal taps, which necessitates a more acceptable solution. The technical problems, the risk of introducing infection through the reservoir and the possibility of drug toxicity may have discouraged some. Our experience is more positive. With careful aseptic handling of the reservoir (458 punctures in 45 patients), we were able to limit the instances of meningitis to three, all caused by commensal bacteria. This never required removal of the reservoir. An early diagnosis and combined i.v. and i.vt. antibiotics are essential. Cefradine 50 mg and cefuroxim 30 mg instilled daily in the cerebral ventricles were both well tolerated, resulting in complete recovery with normal functioning of the reservoir.

Technical problems at the time of insertion of the device depend mostly on the experience of the neurosurgical staff. Other failures can originate from choroid plexus tissue enveloping the draintip and eventually obstructing the perforations. Spontaneous displacement of the catheter tip from a position in the lateral ventricle into the brain parenchyma can occur. These rare complications can be corrected. It is conceivable that growth of the brain and skull in infants could contribute to displacement of the cannula.

Some factors are related to a greater risk of developing ML, such as high initial WBC (>25-50 x 10^9/l), LDH >600, T-cell ALL, L3 morphology and an age under 20.[5,32-34] In our small study the importance of the risk factors was not so clear (see Table 1). ML was an initial finding in two patients with B-ALL and in one with T-ALL. An early start of prophylaxis in the other T-cell leukemias could have counteracted the increased risk. The age distribution of the ML cases was remarkable. The median age of patients without previous CNS treatment was 52 years, while in the propyhylaxis group it was 18. However, this does not mean that one age group is more prone to develop ML since the whole prophylaxis group had a median age of 22.

This study suggests some influence of CNS prophylaxis on the duration of the first remission and the survival (Table 3). It is impossible to separate the contributions of additional factors such as the presence of initial ML. The first remission duration is in the range of the results in some other studies in adults with CNS prophylaxis, although the median survival is longer.[11-13] In this respect the results in the L2 and L10-L10M protocols are certainly better,[19,20] but the rate of all CNS relapses is comparable. Furthermore we did not lose patients because of ML. It is unlikely that the difference in length of CNS prophylaxis played a greater role in their more favorable results than did the more intensive systemic therapy.

The response of ML to i.vt. treatment was independent of prior CNS prophylaxis, simultaneous BM relapse or not. When the ML was symptomatic CNS remission duration was shorter (2 months) than when it was asymptomatic (6 months). This is similar to Stewart et al.'s results.[5]

In conclusion it can be emphasized that a CNS prophylaxis regimen must have the flexibility to be repeated, if required. Maintenance presymptomatic treatment via a reservoir is a convenient method. Furthermore i.vt. chemotherapy can treat CNS relapses well. It does not interfere with systemic chemotherapy, because the remaining BM capacity is not compromised, and cranial or craniospinal radiation is seldom necessary. Also neurotoxicity is prevented by leaving the blood-brain barrier intact as long as possible. Intensification of CNS prophylaxis in certain types of ALL or in patients with high WBC counts must be studied. The optimal duration of the prophylaxis has yet to be determined in a randomized trial. Our impression is that half a year will be adequate. A better overall outcome in adults with ALL will depend on the success of prolonging BM remissions.

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CHAPTER 3

EXPERIENCES WITH THE OMMAYA RESERVOIR FOR PROPHYLAXIS AND TREATMENT OF THE CENTRAL NERVOUS SYSTEM IN ADULT ACUTE MYELOCYTIC LEUKEMIA

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Summary *Intraventricular chemotherapy was administered to adult AML patients via an Ommaya reservoir. Twenty-eight patients received central nervous system (CNS) prophylaxis and seven patients were treated for meningeal leukemia (ML). A treatment course lasted at least 6 months. Asymptomatic ML developed in two patients (7%) of the prophylaxis group concomitantly with bone marrow relapse. One of these patients had not completed the standard course. CNS remission could be obtained in all evaluable patients with ML. The easy entrance to the cerebrospinal fluid (CSF) offers the advantage of frequent investigations of the CSF, early diagnosis and treatment of CNS relapses without radiotherapy, and caused little patient discomfort. CNS prophylaxis in this small study seemed to prolong first remission duration slightly. In M4 and M5 subtypes CNS prophylaxis can be valuable.*

INTRODUCTION

The approach towards CNS prophylaxis is less well defined in acute myelocytic leukemia (AML) than in acute lymphoblastic leukemia (ALL). One reason could be the variations in the reported incidence of CNS involvement in AML. Meningeal leukemia (ML) was clinically diagnosed in adults in 2.5 to 17% and in children in as many as 29%.[5,6,12,15,17,18,21,27,28] When cerebrospinal fluid (CSF) was examined at diagnosis the incidence was 4-18%.[4,14] Frequent clinical and CSF investigations during follow-up may lead to an incidence of 20-43.5%.[10,13,26] In autopsy cases leukemic infiltration of the leptomeninges is as frequent in AML as in ALL.[19] For both it increases with longer survival till 60% at one year

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or longer. Some studies could define one or more risk factors for ML such as myelomonocytic or monocytic leukemia (FAB classification M4 and M5), high initial white blood cell count (WBC), serum lactate dehydrogenase (LDH)>600, extramedullary involvement, age <20 years, and chromosomal abnormalities.[6,11,14,22] However, survival seems to be determined more by the length of bone marrow remission than by the presence or absence of CNS relapse.[21,22,26] At the present time, most authors tend to omit CNS prophylaxis in AML, but at the start of our study it was generally accepted that lengthening of remission increased the risk of CNS involvement, so all our AML patients in complete remission (CR) received intraventricular (i.vt.) maintenance CNS prophylaxis. Later on this view was held only for M4 and M5 subtypes and prophylaxis was then restricted to these groups. In addition patients with ML received i.vt. treatment. In all cases we used an Ommaya reservoir. We report on 10 years of experience with this device in AML patients from a single institution.

PATIENTS AND METHODS

Patients

Consecutive patients with M4 and M5 AML received CNS prophylaxis, when they obtained CR. Early in the study patients with other subtypes were also treated prophylactically. When a patient developed ML he was treated with i.vt. chemotherapy, whether or not he previously had undergone CNS prophylaxis. Patient data and risk factors for ML are shown in Table 1.

Systemic treatment

For systemic remission induction 7-day courses of cytosine arabinoside (AraC) and 6-thioguanine (TG) in combination with 3 days of daunorubicin (D) or doxorubicin (A) (TAD or TAA) were given. After achieving CR by 1 or 2 induction courses, consolidation consisted of intermediate dose AraC, and TG and A. Until 1980 maintenance courses were given with either AraC and TG for 5 days or A for 2 days. From 1980 onwards no maintenance therapy was used. For patients who failed to achieve CR with TAA or TAD, etoposide (VP-16) was added to AraC and A. In case of a systemic relapse reinduction followed the same schedule. Patients with meningeal relapse without signs of systemic relapse received TAA. Five patients had an allogeneic bone marrow transplant (BMT) at our center or elsewhere.

Insertion of Ommaya reservoir

For prophylaxis the device was inserted as soon as the platelet count permitted after reaching CR, usually within 1 to 2 weeks. Before placement of the reservoir the lumbar CSF was analyzed for cell count and cytology. The requirement for a diagnosis of ML was the presence of blast cells in the CSF or clinical signs of meningeal disease, which could not be explained by infection or otherwise together with a pleiocytosis over 5 cells/mm^3. When ML was evident the reservoir was placed within 24 h, and used immediately. At the time of placement the patient received cotrimoxazol for 3 days.

Table 1. Patient characteristics

	CNS prophylaxis		ML
Number	28		6
Sex m/f	18/10		4/2
Age yrs.	17-73		19-57
median	42		36
M1/M2/M3/M4/M5	13/3/2/7/3 (2)		1/1/-/3/1
Initial WBC x 10^9/l			
< 25	19	(1)	2
> 25	9	(1)	4
Initial platelets x 10^9/l			
< 20	6		2
> 20	22	(2)	4
Serum LDH U/l			
< 600	14	(1)	3
> 600	14	(1)	3

ML: meningeal leukemia, number of patients developing ML in parentheses

CNS Prophylaxis

Twenty-eight adults with AML received prophylactic i.vt. chemotherapy, consisting of 100 mg AraC six times every 4 weeks. A few patients received 15 mg methotrexate (MTX) instead of AraC. During systemic relapse CNS prophylaxis was resumed immediately.

Treatment of ML

Seven patients were treated for ML. One of them had received prior CNS prophylaxis. In six patients without prior CNS therapy, meningeal involvement was diagnosed at presentation in one, during systemic remission in another, simultaneously with bone marrow (BM) relapse in two and shortly after systemic relapse in two patients. Three patients were asymptomatic. In addition to ML a leukemic cerebral mass was diagnosed in one and a spinal epidural mass in another patient. The ML patients received i.vt. AraC or MTX every 4-5 days, without radiotherapy. MTX levels in the CSF were monitored. An alternating scheme was sometimes used to avoid accumulation of MTX. After clearing the CSF of blast cells and attaining a stable neurological condition, consolidation consisted of four weekly and two biweekly injections. Maintenance was administered six times every 4 weeks. When a CNS relapse was diagnosed the cycle started again. Intracerebral and epidural tumor were treated with radiation (up to 25 Gy.).

RESULTS

Efficacy of CNS prophylaxis

Two out of 28 patients developed asymptomatic ML, simultaneously with BM relapse. Both had M4 type AML. One of them had refused part of the prophylaxis; he was not treated for relapse. Relapse and survival data are given in Table 2.

Table 2. Results of CNS prophylaxis and treatment of ML

	CNS prophylaxis					ML no prophylaxis
		relapse				
	total	BM -	BM +	CNS -	CNS +	
Number	28	6	22	26	2	6
alive in CR	6	6	-	6	-	1
1st rem. duration	9 (3-94+)	87+ (26+-94+)	8 (3-36)	9 (3-94+)	7 (7,8)	5 (4-21+)
Survival	22 (8-98+)	90+ (30+-98+)	16 (8-53)	22 (8-98+)	16 (16,46)	16 (12-24+)

BM: bone marrow, CNS: central nervous system; CR: complete remission;
+ or -: dissemination present or absent;
median value in months, range in parentheses

Efficacy of ML treatment

Of eight patients with ML two had received prior CNS prophylaxis. Seven of them were treated. Six patients attained CNS remission, while in one patient survival was too short to evaluate the result of i.vt. treatment. Shortly before death positive CSF findings or mild clinical signs were again present in two patients. Permanent CNS remission persisted in three others until death, while one patient was still free of CNS disease after 4 months, when the study was closed. Median survival was 5 months from the time of the first CNS relapse, 12 months being the longest period. Death was never caused by ML. Systemic relapse, hemorrhage and infection were the major death causes.

Complications

The implantation of the Ommaya reservoir caused a neurological deficit once, although CSF was easily obtained from the reservoir peroperatively. After repositioning of the draintip this cleared completely.

Bacteria were found in the CSF five times in four patients, and based on this finding meningitis was diagnosed. The symptoms were always mild. Nuchal rigidity or focal signs were never encountered. Once a postoperative asymptomatic infection developed. In two cases the infection could be related to puncturing the reservoir. The remaining two episodes were "spontaneous" during a phase of severe leucopenia. The patient with the postoperative infection suffered a period of "spontaneous" meningitis 3 years after the first attack. It was caused by an identical bacterium. As causative organisms diphteroid bacillus (3) and staphylococcus epidermidis (1) could be isolated from the CSF cultures. One Gram positive bacillus did not grow in culture. A weeklong course of cefradine 50 mg i.vt. daily and 2 g i.v. tid. was successful in all cases. The devices were left in place and could be used normally afterwards.

Only one case of serious neurotoxicity was seen in a patient who received a BMT elsewhere. On return to our hospital the ventricular CSF MTX level was markedly elevated (1.14×10^{-4} M/l). Three weeks later a myelopathy was the first sign of MTX caused damage, followed by brainstem symptoms. Cognitive functions were not impaired. Progression slowed down after 3 months.

The Ommaya reservoir remained in place for the rest of the patient's life. Apart from the episode of meningitis after 3 years in one patient as mentioned above, no other device-related complications were seen. The reservoir proved to be patent even after as many as 8 years.

DISCUSSION

The need for CNS prophylaxis in AML is a controversial issue.[16] In some studies the incidence of ML was reported to be less than 12%. This can partly be due to the effect of including AraC in the treatment schedule, but also to the lack of routine neurological exams and spinal fluid studies and to the time at risk. Furthermore earlier studies have demonstrated that complete remission can be terminated by CNS relapse and the incidence of this complication is related to the time at risk.[3,7,8,25,27,28] In a study of children, patients were randomized to receive either craniospinal radiation or not. Relapses in the CNS were prevented, but survival in the radiation group was not prolonged.[4] In one study of adults the incidence of ML was influenced by intrathecal prophylaxis,[22] while in another it was not.[20] In the latter the start was rather late and the duration relatively short.

The advantages of administration of CNS prophylaxis via an Ommaya reservoir have been discussed by us elsewhere.[9] Although AraC is the drug of choice for AML, drug resistance sometimes forces the use of MTX. Use of the Ommaya reservoir has been a disappointment in some studies. However, with proper precautions including aseptic handling, drug level monitoring, injecting slowly and early treatment of an inadvertent infection, it has several advantages. It enables frequent CSF analysis as well as long-term and repeated prophylaxis and treatment. Distressing symptoms of ML can also be prevented. Radiation therapy can be avoided in most cases. In our opinion complications are acceptable in frequency and severity and do not argue against the use of an Ommaya reservoir.

Our patient population was too small to draw firm conclusions about the efficacy of our strategy, but the incidence of ML in the prophylactically treated patients was low in comparison with other studies without prophylaxis,[10,13,26] and approaches the results in children with craniospinal radiation as prophylaxis.[4] In one of the two patients who developed ML only part of the CNS prophylaxis was given because of refusal by the patient. The other patient had a M4 type and an initial WBC of $371 \times 10^9/l$ as risk factors. We had no primary CNS relapses. Some of the patients received total body irradiation for BMT and this undoubtly could influence the final outcome. ML was diagnosed between 0 and 45 months (median 11 months) from initial diagnosis. This is in agreement with studies in which ML was also a relatively late manifestation.[1,21] Why in other series it comes about early is not easily understood.[4,13,22] Most of our patients who developed ML belonged to the M4 and M5 subgroups. Of those who had not received prophylaxis only one (M5) had initial ML. Of the three M4 patients who had not received CNS prophylaxis, one was a referral from another hospital; in the second initial subtyping was uncertain and the third dated back to the period prior to the introduction of CNS prophylaxis for AML.

Our approach seems also effective for treatment of ML, in that all patients responded satisfactorily, and four of them permanently. A note of caution should be added for neural parenchymal infiltration besides ML, as occurred once in our population. It is questionable whether therapy directed to the leptomeninges could have prevented or cured this event. Diffusion of MTX in the brain parenchyma is limited and levels are not high enough to eradicate leukemic cells deep in the brain. AraC penetrates even less than MTX.[2]

One would like to see that CNS prophylaxis could influence remission duration and survival. This seems not to be the case, since survival is primarily determined by the length of BM remission.[21,22,26] Median survival in our ML patients was 16 months versus 13 in a comparable group.[21] The median duration of first BM remission was somewhat longer for those with prophylaxis compared to those without, but numbers are small. However, this has also been observed by others.[21,24]

Although ML was never a cause of death, the median survival after diagnosis of the first CNS relapse was only 5 months (symptomatic 5 months, a-symptomatic 7 months). This was the same as in other series.[21,23] According to Stewart prospects of success in attaining CNS remission and in preventing further CNS relapses differ, depending on whether the patients were asymptomatic or symptomatic.[22,23]

More effective treatment of bone marrow disease will be needed to better the overall outcome in AML. As long as no better disease control is available we suggest that CNS prophylaxis has a place in AML of the M4 and M5 type, because six monthly i.vt. injections of AraC reduce the incidence and thus the morbidity of ML and possibly lengthen first remission duration. I.vt. chemotherapy is also appropriate treatment for ML. Whether systemic high dose AraC would be sufficient for prophylaxis must be determined.

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CHAPTER 4

RESULTS OF INTRAVENTRICULAR CENTRAL NERVOUS SYSTEM PROPHYLAXIS AND TREATMENT IN NON-HODGKIN'S LYMPHOMA

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Abstract *In 47 adult patients with non-Hodgkin's lymphoma an Ommaya reservoir was inserted. In 27 patients placements and subsequent intraventricular (i.vt.) treatment were prophylactic. A primary central nervous system (CNS) relapse was seen in one of 27 patients (3.7%). Meningeal lymphoma developed in 26 patients, 20 without and 6 with prior CNS prophylaxis, mostly (90%) during active systemic disease. I.vt. treatment resulted in neurological improvement or stabilization in 73%, including 38% complete CNS responders. An Ommaya reservoir facilitates drug administration into the CSF. This form of treatment is well tolerated and is applicable on an out-patient basis.*

INTRODUCTION

Central nervous system (CNS) relapse in Non Hodgkin's lymphoma (NHL) mostly occurs in the form of meningeal lymphoma (MenLy). Meningeal involvement especially concerns the high grade malignant lymphomas and is less frequently seen in low grade malignant lymphomas.[5,12,18] MenLy may develop in approximately 40% of lymphoblastic lymphoma (LBL) and in 10-12.5% of immunoblastic lymphoma (IBL).[4,9,31] Apart from histologic subtype other risk factors are bone marrow (BM) involvement, extranodal disease, age < 35 years, T-cell markers and poor response to initial therapy.[5,20,23,25] Although CNS prophylaxis is considered necessary in LBL by most authors[5,14,21] there is no agreement which other subgroups of NHL may benefit from CNS prophylaxis, nor on the treatment of choice and the optimum dose and duration.[11,20,34] Cranial radiation has long been the mainstay of CNS prophylaxis. Intrathecal (i.t.) chemoprophylaxis alone was also able to prevent isolated CNS relapses in acute lymphoblastic leukemia (ALL) and LBL.[29,31] However this method was

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insufficient in preventing CNS relapses in children with T cell ALL with features of lymphoma in one series.[26]

Intraventricular (i.vt.) administration of drugs through an Ommaya reservoir offers an advantage since the distribution of the drug in the cerebrospinal fluid (CSF) is more reliable than with lumbar i.t. injections.[27] Direct i.vt. entrance to the CSF is supposed to establish a more effective CNS prophylaxis and the use of cranial radiation, which increases the risk for the development of leukoencephalopathy can be avoided.[10,22]

From 1976 we have used i.vt. chemotherapy for CNS prohylaxis and MenLy treatment in NHL patients. Our 10 year single institute experience with this method forms the basis of this report.

PATIENTS AND METHODS

Patients belonged to two groups: (1) those qualifying for CNS prophylaxis; (2) those who developed MenLy, either without or with prior CNS prophylaxis.

Diagnosis and systemic treatment of NHL

Patients were clinically staged according to standard procedures and classified according to the Ann Arbor criteria.[2] For histo-pathologic typing the Kiel classification was used.[16] The Working Formulation was used to divide the subtypes in low, intermediate and high grade malignant lymphomas.[33] The polymorph centroblastic lymphoma (CBL) of the Kiel classification is considered to be high grade malignant.[24] Systemic treatment of NHL varied from 1976-1986 according to histologic subtypes and ongoing protocols. In short: LBL was initially treated with vincristine, doxorubicin and prednisone; from 1984 onwards VP16-213 and cytosine arabinoside (AraC) were added. Bulky mediastinal disease in LBL was treated with additional radiotherapy. After remission, standard ALL maintenance was given for 3 years. Five out of 23 patients with LBL received an allogeneic bone marrow transplant. Other high grade NHL received either (M)CHOP-like regimens or were enrolled in an ongoing phase II trial, incorporating methylprednisolone, methotrexate (MTX), AraC and high dose cyclophosphamide with doxorubicin.[13]

Complete systemic remission (CR) was defined as the disappearance of all measurable tumor, persisting for a minimum of one month after completion of induction therapy. A partial remission (PR) was defined as more than 50% reduction in tumor size which lasted for a minimum of one month. All other patients were considered non-responders (NR). An isolated CNS relapse formed an indication to resume systemic treatment.

CNS prophylaxis

An Ommaya reservoir was inserted after attaining CR or during induction therapy in consecutive patients with LBL independent of stage. In patients with IBL or polymorph CBL an Ommaya reservoir for prophylaxis was placed before 1984 when they had advanced disease and afterwards only when BM involvement or T cell markers were present. CNS prophylaxis consisted of 15 mg MTX i.vt. every 4 weeks for 6 times. The CSF was examined regularly for cell count and cytology. CNS prophylaxis was reiterated during a systemic relapse, and continued during progressive disease.

CNS treatment for MenLy
MenLy was defined as the presence of lymphoma cells in the CSF or of 5 or more mononuclear cells per mm^3 together with clinical signs of meningeal disease responding to CNS chemotherapy. Treatment for MenLy consisted of 15 mg MTX i.vt. every 4 days or alternatingly MTX and AraC, till CNS response was obtained, defined as clearance of the CSF and improvement or stabilization of the neurological abnormalities. The MTX dose was adjusted to the level in the CSF. After attainment of a CNS response patients received 4 weekly and 2 biweekly injections, followed by instillations every 4 weeks for 6 times. Radiotherapy was added only for intracerebral or bulky dural disease or for progression of MenLy during i.vt. chemotherapy.

RESULTS

Between 1976 and 1986 an Ommaya reservoir was inserted in 47 patients. The clinical status of the patients is documented in Table 1.

Table 1. Patients receiving i.vt. CNS prophylaxis or treatment

		CNS prophylaxis	CNS treatment
Number		27	20
Age (yrs)	median	26	36
	range	15-63	14-81
Stage	I	-	3
	II	8	2
	III	4	-
	IV	15	15
Histopathology*:			
low grade		-	2
intermediate gr.		-	4
high grade		27	14
CBL,IBL,UDL		8	10
LBL		19	4

*Kiel classification/Working Formulation, CBL:polymorph centroblastic-, IBL:immunoblastic -, UDL:undefined -, LBL:lymphoblastic lymphoma

Patients receiving CNS prophylaxis: (see Table 2).
Prophylaxis was given to 27 patients. MenLy developed in 7 patients (26%). Only one patient had a primary CNS relapse (3.7%). This was a case of CBL. The other 6 patients had LBL : MenLy was seen during induction treatment despite early initiation of CNS prophylaxis in 2 cases; in 3 patients MenLy

Table 2. Risk factors and development of meningeal lymphoma

	PROPHYLAXIS		NO PROPHYLAXIS
	no meningeal lymphoma	meningeal lymphoma	meningeal lymphoma
Number	20	7	20
Histopathology			
low gr.			2
intermed.gr.			4
high gr.			
CBL,IBL,UDL	7	1	10
LBL	13	6	4
Initial positive BM/PB	9 (45%)	5 (72%)	11 (55%)
Systemic disease activity			
PR or NR or			
syst.relapse	9 (45%)	7 (100%)	18 (90%)
1st Remission duration	41+ (3-109+)	4 (4-15)	8 (2-90+)
Survival	40+ (6-113+)	11 (4-52)	11 (2-91+)

PR: partial systemic remission, NR: non responder,
BM: bone marrow, PB: peripheral blood,
rem.duration and survival: median value in months, range in parentheses

developed during therapy for systemic relapse, but in two of those patients CNS prophylaxis had not been reiterated; one other patient had positive CSF cytology shortly before death. Thus active systemic disease was present in 6 of 7 patients (86%) at the time MenLy was detected. Six patients were subsequently treated for MenLy.

Patients with MenLy but without CNS prophylaxis: (see Table 2 and 3).
MenLy was diagnosed from 0 to 84 months from the initial diagnosis of NHL in 20 patients. The diagnosis was made at first presentation in 3 patients, during early treatment before systemic CR in 2, at the same time as systemic relapse in

Table 3. Development of meningeal lymphoma and results of treatment

	PRIOR CNS PROPHY-LAXIS	NO CNS PROPHY-LAXIS	TOTAL
Number of patients	7	20	27 (100%)
Development of MenLy			
at diagnosis	-	3	3 (11%)
during treatment for active systemic disease (induction,relapse, palliation)	6	12	18 (67%)
at syst.relapse	-	3	3 (11%)
during CR	1	2	3 (11%)
months from diagnosis or relapse	2 (0-11)	2 (0-64)	2 (0-64)
Results of treatment			
duration 1st CNS response	14 (2-15)	4 (1-90+)	5 (1-90+)
survival from diagnosis MenLy	7 (0-39)	3 (0-91+)	3 (0-91+)

MenLy: meningeal lymphoma, CR: complete systemic remission,
CNS response and survival : median value in months, range in parentheses

3, during treatment of a systemic relapse in 3 and in 7 non- or partial responders. Two further cases were seen during CR. Thus MenLy developed during active systemic disease in 18 of 20 patients (90%).

MenLy, symptomatology and results of CNS treatment: (see Table 3).
Of the 27 cases with meningeal involvement (including 6 patients with prior prophylaxis), 5 were asymptomatic. Deficits of the cranial nerves or spinal roots or an elevated intracranial pressure were equally frequent in presentation. Epidural disease, which was considered to be part of systemic disease, was initially present in 1 patient with MenLy and in 2 patients receiving prophylaxis. The latter did not develop MenLy. Besides MenLy one patient had an intracerebral deposit and another a dural mass in the cavernous sinus. Median time from diagnosis or relapse of systemic disease till the development of MenLy was 2 months.

Twenty-six patients were treated. Two patients with progressive resistent systemic disease died within 2 weeks. Complete CNS response was attained in 10 patients (38%); additional radiation therapy was needed in 2 cases. Overall improvement or stabilization of clinical signs of MenLy was seen in 19 out of 26 treated patients (73%).

Of the 10 complete CNS responders 4 patients remained in CNS remission. A total of 11 CNS relapses occurred in the 6 other complete responders, but in all except one the systemic disease was active at CNS relapse. Only one patient with MenLy is a longterm disease free survivor. In this case MenLy was detected at presentation.

Complications

In one of the 47 patients insertion of the reservoir caused a mild neurologic deficit, which was reversible after correction of the drain position. Leucoencephalopathy did not develop during prophylaxis and was only seen in one patient on i.vt therapy for 3 years, who also had received cranial radiotherapy for intracerebral tumor. His symptoms disappeared when MTX was substituted by AraC.

Meningitis, which was seen in six patients, was asymptomatic or signs were limited to fever or a mild headache. These infections have not led to major complications and were without sequelae. An infection of the meninges was always related to reservoir puncturing. The total number of injections and diagnostic punctures in the device was over 600. Permanent skin flora bacteria were the causative agents. Intravenous (i.v.) and i.vt. cefuroxim or cefradine controlled infection in all cases except one. Although this patient had no complaints the reservoir was removed and after another course of antibiotics a new one was implanted without infection recurrence.

DISCUSSION

For CNS prophylaxis in unfavorable histology NHL i.t. chemotherapy during a short period or as maintenance has been recommended.[7,15,22,31] Others have advocated the use of cranial radiation[17,19,32] or i.v. chemotherapy (AraC or high dose MTX).[21,25,28] CNS prophylaxis was less effective when started late in the course of the disease.[3] Our i.vt. prophylaxis was limited to 5 months, but with the possibility to repeat it at times of systemic relapse. When systemic disease was progressive, prophylaxis could be prolonged indefinitely. The incidence of primary CNS relapse in our patients receiving i.vt. prophylaxis was 3.7%. This is in keeping with results in children receiving i.t. prophylaxis for NHL.[1,30]

The question arises whether CNS prophylaxis could have prevented meningeal involvement in the 20 patients who originally received systemic treatment

only. Eleven patients did not qualify according to our inclusion criteria; in 5 patients MenLy was already present very early; 2 patients did not respond to induction therapy, postponing the insertion of the reservoir, and in 2 patients initial histology was not conclusive. Our results suggest that patients with all stages of high grade malignant lymphoma irrespective of BM status, as well as patients with intermediate grade histologies with a positive BM and patients with epidural deposits may benefit from CNS prophylaxis. The inclusion of patients with epidural disease is also recommended by Mandell.[22]

MenLy had a high incidence among LBL patients (10/23 patients: 44%). Prophylaxis was intended for all LBL cases, but MenLy was an initial or very early event in 4 patients (17%), and in the other 6 patients MenLy occurred during treatment for relapse or palliation, including 2 patients in whom prophylaxis was not repeated. These results suggest that early and more intensive preventive treatment is needed in patients with LBL, e.g. more frequent i.vt. MTX or MTX alternating with AraC. Resuming the prevention during a systemic relapse should be adhered to strictly.

The mainstay in the prevention of MenLy remains control of systemic disease, e.g. by using more intensive systemic therapy.[28] MTX and AraC penetrate into the CSF only when given in high doses.[6,8] The systemic toxicity of these high doses is considerable. Therefore, to prevent the serious morbidity of meningeal disease, CNS prophylaxis directly administered into the CSF seems more attractive. The i.vt. route is a convenient one, is acceptable to the patients and can be used on an outpatient basis. With diligent use the method has a low complication rate. Leucoencephalopathy does not develop during prophylaxis, and this complication will seldom be seen with MenLy treatment when MTX levels in the CSF are monitored. The instances of infection in less than 1% of the procedures occurred mostly in the early years of the study. They could often be traced back to violation of the aseptic procedures during reservoir puncturing. Strict aseptic techniques for transcutaneous access will prevent iatrogenic infections via the Ommaya reservoir. Antibiotics nearly always succeed in clearing the device of an unintentional infection.

Meningeal disease contributed substantively to the direct cause of death in 16 NHL patients, in contrast to our experience with an identical regimen for CNS treatment in ALL.[10] A CNS remission was obtained in all cases of meningeal leukemia treated with i.vt. therapy. The possibility to control overt meningeal dissemination in NHL with a more frequent use of multiple i.vt. agents should be investigated. Adding cranial radiation to the i.vt. regimen will not solve this problem, as most patients with MenLy will have active systemic disease and therefore the CNS remains continuously at risk.

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CHAPTER 5

NORMAL CEREBROSPINAL FLUID DYNAMICS EVALUATED BY INTRAVENTRICULAR INJECTION OF ^{111}IN-DTPA

A study in leukemia and lymphoma patients without meningeal involvement.

Hanny Haaxma-Reiche*, Do Albertus Piers** and Henk Beekhuis**

Abstract *The cerebrospinal fluid flow pattern in seven patients with leukemia or lymphoma, but without prior meningeal or cerebral disease is studied following introduction of ^{111}In-DTPA in a lateral ventricle through an Ommaya reservoir. The time to egress from the ventricular system into the basal cisterns was variable, but generally short. One hour after administration the basal cisterns were clearly visible in all patients. Thereafter kinetics throughout the cranial and spinal subarachnoid space were consistent. The flow patterns of three patients cured of meningeal dissemination and one patient with mild meningeal leukemia were similar to the normal pattern.*

INTRODUCTION

The cerebrospinal fluid (CSF) flow pattern can be visualized by scintigraphy. Although injection of the radiopharmaceutical at the lumbar level introduces an artifact in the normal CSF circulation, such studies have contributed to the knowledge about normal and pathologic CSF pathways. To study the CSF flow from the source downwards, one needs introduction in a lateral ventricle.[1] Access to the cerebral ventricles of human individuals without meningeal or intraparenchymal disease is seldom available. The patients of Di Chiro et al. were as close as possible to normal, because they were in central nervous system (CNS) remission of malignant meningeal involvement, after cranial radiotherapy and/or intraventricular chemotherapy.[2] Because in our hospital adult patients in systemic remission of acute lymphoblastic leukemia, of some

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subtypes of acute myelocytic leukemia and high grade malignant non-Hodgkin's lymphoma receive CNS prophylaxis via an Ommaya reservoir, we had the opportunity to study the CSF flow in patients who were truly neurologically normal.[3] The results were compared with flow studies in patients cured of meningeal dissemination and in one patient with overt meningeal leukemia.

PATIENTS AND METHODS

Patients

Scintigraphy of the cerebral ventricles and the subarachnoid space was performed in 10 adult patients (age:16-62 years) with hematopoietic malignancies. All patients had a subcutaneous reservoir with a ventricular catheter inserted. Seven patients were free of neurologic involvement prior to the investigation. CSF was completely normal and CSF pressure was not elevated. Cytology of the ventricular CSF prior to the examination was always negative for malignant cells. CT scans showed ventricles, cisterns and sulci within the normal range. In most patients the scintigraphic study was done several days postoperatively. In two the interval was longer (1-33 months). These patients had received prophylactic intraventricular chemotherapy for one to six times. Radiotherapy was never administered. Three patients were in CNS remission of meningeal dissemination at the time of the study. Two of them had experienced neurologic signs and one had been asymptomatic, but neurologic signs had cleared and CSF had normalized after treatment with 8 to 13 doses of intraventricular chemotherapy. In addition one patient, who initially belonged to the normal patient group, was reexamined when suffering from overt meningeal leukemia. Intracranial pressure was then elevated (30 cm H_2O). Procedures were performed after obtaining informed consent.

Methods

The procedure was standardized as follows: The reservoir was punctured with a 25 gauze needle with the patient in the supine position. Nine ml of CSF was removed equalizing the volume to be injected. A dosage of 18-25 MBq (0.5-0.7 mCi) of ^{111}In-DTPA in a volume of 6 ml was injected, followed by a flushing volume of 3 ml saline 0.9%. All volumes were chosen as to be similar to the amounts involved in our regular procedure of intraventricular administration of chemotherapeutic drugs. Images were obtained using a large field of view gamma camera with a medium energy parallel-hole collimator. An anterior and a lateral view of the skull and upper cervical region were made immediately after injection of the tracer (t=0 h), after flushing with saline at 0.2 h, and at 1, 4, and 24 h after the initial injection. In two cases images were also obtained after 48 h. Simultaneously digital images were stored in a computer. Images of the spinal canal were only obtained at 1, 4 and 24 h. The patient remained supine for the first hour.

Analysis

Images were reviewed for the circulation in the ventricular system, the cranial and the spinal subarachnoid space. The digital images were studied for the amount of radioactivity using standard region of interest techniques. These data were used for calculating the disappearance of the radioactivity from the skull. The mean of the counts in the anterior and the lateral view of each pair of images was calculated and, after correction for physical decay, presented as the percentage of the value obtained

immediately after injection of the tracer. For each patient the residence time of the tracer was calculated as the area under the disappearance curve after extrapolating the data from t = 0 h to infinity, using the 4 and 24 h data points.

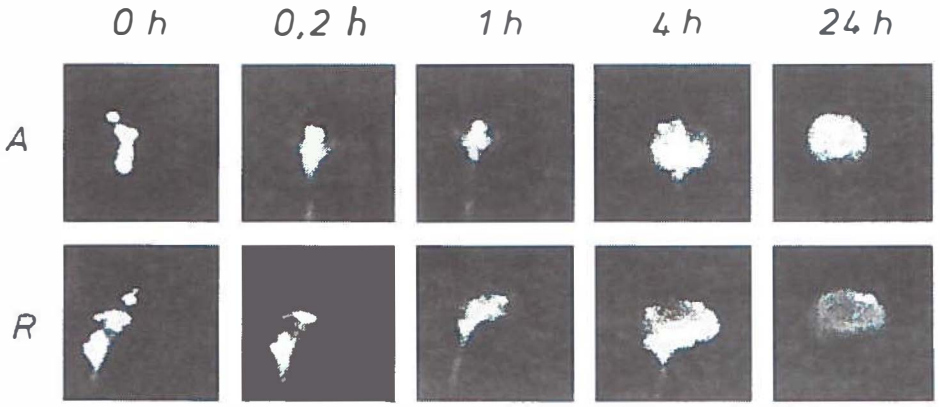
RESULTS

In the seven patients without CNS dissemination at any time prior to the investigation, a rather consistent pattern of CSF flow was found (fig.1). Immediately after injection and flushing, radioactivity was present in the homolateral ventricle and in the third ventricle region in all cases. The one hour post-injection images revealed the same pattern and in addition substantial transport into the contralateral ventricle in 3/7 patients, and a beginning of passage in 2/7 patients. Basal cisterns began to fill nearly immediately, shortly thereafter followed by the upper cervical subarachnoid space. Both were clearly visible 1 hour after injection. Early imaging of the lumbar sac was seen at 1 h, and filling was evident within 4 hours. Radioactivity could rarely be seen in the subarachnoid space above the tentorium before 1 h. At 4 h the lower part of the cerebral convexity was reached. Ascent continued over the cerebral hemispheres and the 24 h images showed a homogenous distribution over the whole CSF compartment. Over the next 24 hours the radioactivity diminished. In fig.1a the intensity of the images up to 1 h is not mutually comparable with that of the later ones, but is chosen for better illustration. These pictures represent the sheer distribution of the radioactivity, as seen in all subjects.

At 1 h post-injection 40-99 % of radioactivity was retained intracranially and at 4 h 25-98% was still present (fig.2). The disappearance rate on the second day was the same as between 4 and 24 h. The calculated residence times in the normal subjects varied from 8 to 41 hours, with a mean of 24 hours. The results in a patient with overt although mild meningeal leukemia and in three patients in CNS remission after treatment for meningeal dissemination are also shown in fig.2. The residence times in these four patients were respectively 15, 28, 51, and 55 hours.

Fluid flow interruptions like obstructions within the ventricles, in the spinal canal or at the convexities were not encountered in these last four patients.

Flushing cleared the Ommaya reservoir completely in 7/11 trials. In the other instances minimal radioactivity remained visible at that site. At 24 h the region of the device was outlined again in 8/11 patients. The amount of radioactivity at that site was then quite variable.



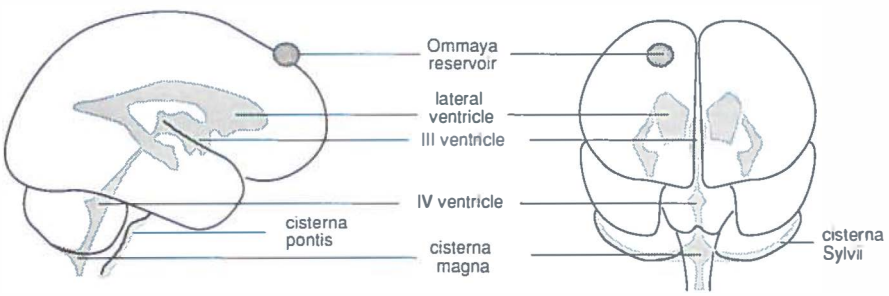


fig.1: (a) CSF kinetics of intraventricular injected ^{111}In-DTPA: anterior (A) and right lateral (R) view, after injection (0 h), after flushing (0.2 h) and at 1, 4 and 24 h
(b) Schematic anatomical drawing with position of Ommaya reservoir

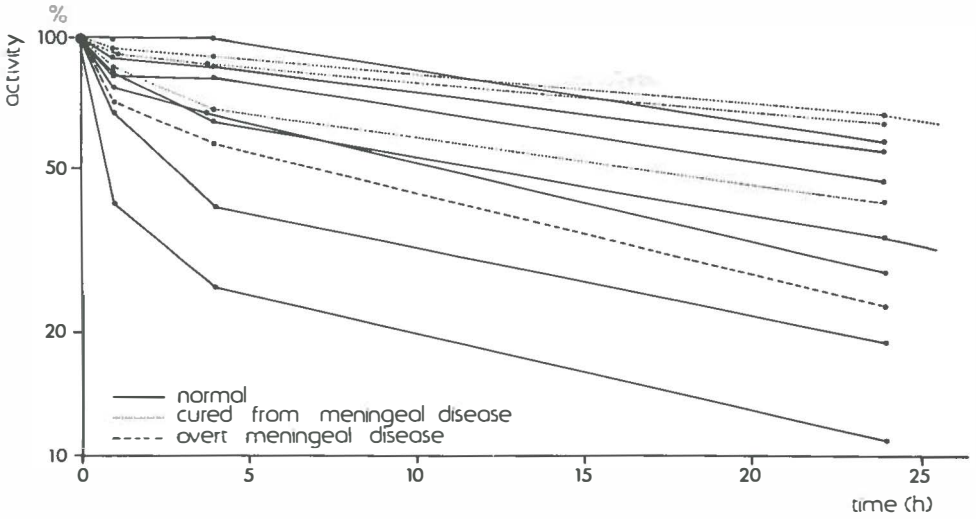


fig.2: Whole skull disappearance curves of intraventricular injected ^{111}In-DTPA in 11 procedures.

DISCUSSION

Up till now CSF flow from the ventricular source onwards has been studied in subjects with prior involvement of the meninges or the CSF pathways.[1,2] Most of these cases were only followed for 3,5-4 hours. In our study seven of the subjects were completely free of neurologic signs and symptoms, and had normal CSF and CT findings.

The third ventricle filled shortly after the lateral ventricle. Outflow from the ipsilateral ventricle into the basal cisterns showed some variations between individuals. In some patients passage was already present before flushing, in others this occurred after flushing, but filling was completed at 1 h in all cases. The cervical subarachnoid space filled consecutively to the basal cisterns. Entrance in the contralateral ventricle was noted, although at a somewhat slower pace than the flow out of the foramina of Luschka and Magendie. That this was not seen in all patients may be due to the long interval between the 1 and 4 h pictures. Ascent in the subarachnoid space begins during that period and can obscure the structures situated in the midline. Later it becomes difficult to distinguish between the different components of the now more diffuse intracranial image (fig.1). Downward flow into the lumbar dural sac was substantial at 4 h. This is in keeping with the findings in a study in which methotrexate (MTX) distribution was investigated. Four hours after administration in the Ommaya reservoir the lumbar CSF concentration of MTX reached a

maximum.[4] Ascent from the basal cisterns in the lateral direction around the cerebral convexities and along the medial routes through the suprasellar cistern or the quadrigeminal cistern into the pericallosal and inter-hemispheric cisterns was the slowest part of the transport.

The pattern of CSF flow dynamics in subjects free of CNS disease, the pattern in patients cured of symptomatic, but not severe meningeal leukemia/ lymphoma and the pattern in a patient with overt but mild meningeal leukemia were not essentially different. These findings resemble those of Di Chiro in patients cured of meningeal involvement[2].

The influence of the patients position was not investigated, because we choose not to impose special restrictions. However in experiments with monkeys no influence of various positions has been found.[2]

An influence of the frequency of chemotherapeutic drug administration on the ultimate CSF flow was not established. Normal subjects had received one to six doses of prophylactic chemotherapeutic drugs and patients cured from meningeal disease were treated with up to 13 injections.

Flushing with 3 ml succeeded in clearing the reservoir, in the meantime making barbotage procedures unnecessary. The late reappearance of the reservoir site doesn't signify reflux, but is explained by diminished cicatricial resorption around that site. This behavior is comparable with the experiences with leptomeningeal cysts.[5]

Quite often the question arises whether intrathecal drugs are effective enough for meningeal dissemination. Several factors will be contributive, among others the time a drug is present in sufficient concentration in the CSF and the distribution of the intrathecal drugs. Both are dependent on the CSF flow. MTX and cytosine arabinoside, the drugs most often used for meningeal leukemia and lymphoma, are mainly eliminated by CSF bulk flow and only for a limited amount by diffusion.[6] Over the brain convexities absorption occurs through the arachnoid villi into the dural sinuses.

The area under the disappearance curve (fig.2) can be considered as a measure for the exposure time of the CSF spaces and its linings to the tracer and probably in a similar way to chemotherapeutic drugs like MTX. The area varied over a wide range. This variation was mainly caused by the large differences in the disappearance rate of the tracer from the intracranial CSF space during the first hours after administration. This seems related to the speed with which the tracer entered the spinal region. Thereafter kinetics from the basal cisterns upwards and the rate of elimination from the cranial subarachnoid space were rather similar in all patients.

The CNS spread of haematopoietic malignancies tends to be diffuse and multifocal in the meninges and also to involve the ventricular linings. The ventricular system is not well reached by lumbar injection of radiopharmaceuticals[7], while ventricular MTX levels after lumbar injections are often inade-

quate or unreliable.[4] Therefore intraventricular drug administration should be favored over lumbar injections, since the former has the advantage that the total ventricular system will be reached.

The identical CSF flow patterns in our different categories may mean that a reliable distribution of intraventricularly introduced chemotherapeutic drugs can be assured throughout the CSF space in normal subjects, in patients with early stage meningeal dissemination and in patients cured of this involvement.

It has been established that widespread involvement of the meninges will obstruct the CSF pathways either by blocking the ventricular outflow, the upward flow over the convexities and downward flow in the spinal canal, or by preventing resorption through the arachnoid granulations.[1,8]

It must still be defined how severe neurologic symptomatology has to be, before CSF kinetics become disturbed. Patients with symptomatic meningeal leukemia, but at an early stage of meningeal dissemination may have a normal distribution, so it is worthwile to start drug treatment first and use radiotherapy only when drug treatment fails. In these patients a radionuclide ventriculography before the initiation of the intraventricular drug treatment can provide an insight in the CSF dynamics and may help in planning the most adequate form of therapy.

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CHAPTER 6

NEUROPATHOLOGICAL FINDINGS

Neuropathological findings could be studied in 19 patients. Autopsy of the nervous system consisted of removal of the brain and the leptomeninges and sometimes the spinal cord. Removal, fixation, staining and sectioning were done according to the standard procedures. Although the available records and slides gave enough information about the individual cases, this material was not suitable for statistical analysis. Often patients died at home and even when they died in the hospital, autopsies were not always requested or were refused. In other instances only body postmortems were performed. Findings are summarized in Table 1.

Five patients had ALL, six patients AML, and eight suffered from NHL. A whole variety of subtypes was represented in these three groups.

As far as the CNS treatment is concerned: prophylactic chemotherapy only was given to nine patients; four patients received initially prohylactic treatment, but later ML or MenLy treatment courses; in the six other cases only meningeal dissemination regimens were administered. In half of these last cases cranial and/or spinal radiation formed part of the treatment.

The available material was reviewed to see whether:

1. CNS prophylaxis was succesful.
2. Therapeutic regimens were adequate.
3. Clinical neurologic assessment and CSF findings on the one hand and postmortem findings on the other hand were in agreement.
4. Neurotoxic side effects of i.vt. therapy could be detected.

Leukemic and lymphomatous dissemination in the CNS

Grading of arachnoid leukemia and lymphoma was done as described by Price and Johnson[1]. The different grades are illustrated in fig.1-5.

Grade 1: Mild to moderate leukemic/lymphomatous infiltration in superficial arachnoid with or without CSF channel contamination and with or without isolated deep cortical arachnoid involvement.

Grade 2: Dense arachnoid leukemic/lymphomatous infiltrate with CSF channel contamination and arachnoid involvement in the deep grey and white matter.

Grade 3: Extensive superficial and deep leukemic/lymphomatous arachnoid involvement, CSF channel contamination and destruction of the pia-glial membrane.

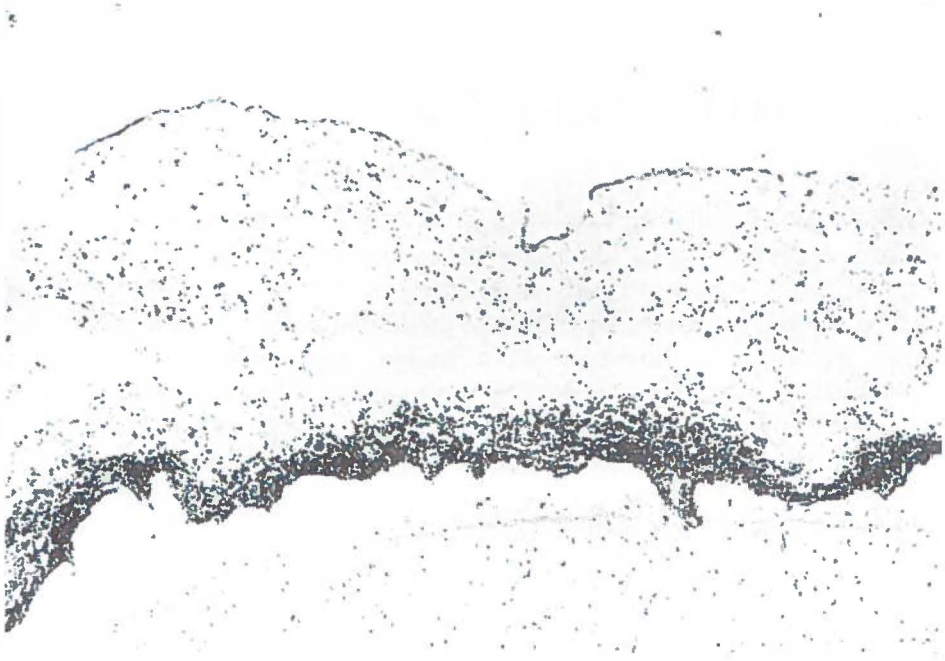

fig. 1: Grade 1 infiltration of the arachnoid over the cerebral cortex

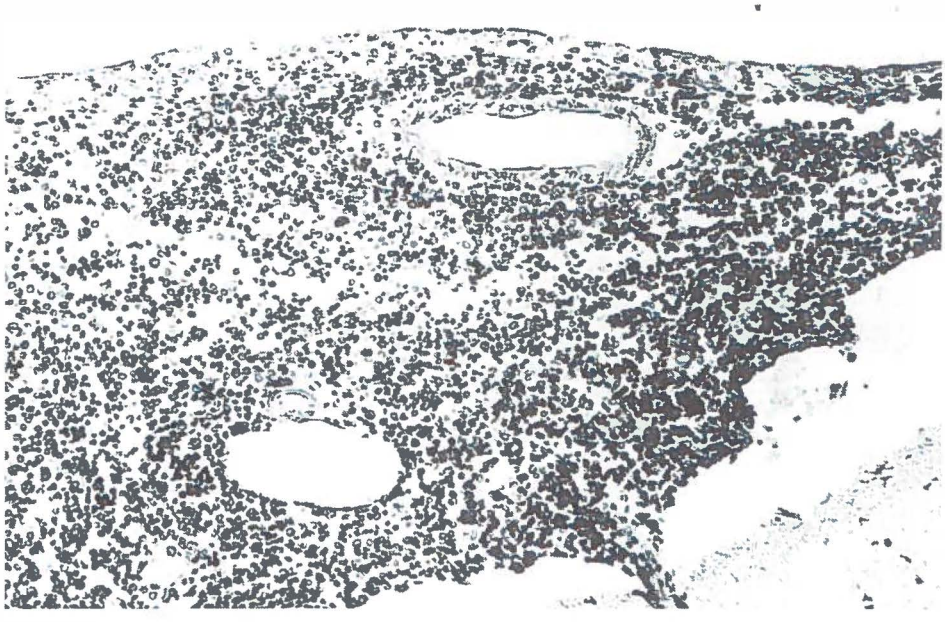

fig. 2: Grade 2 infiltrate in the arachnoid

fig. 3: Grade 2 infiltrate in the depth of a sulcus

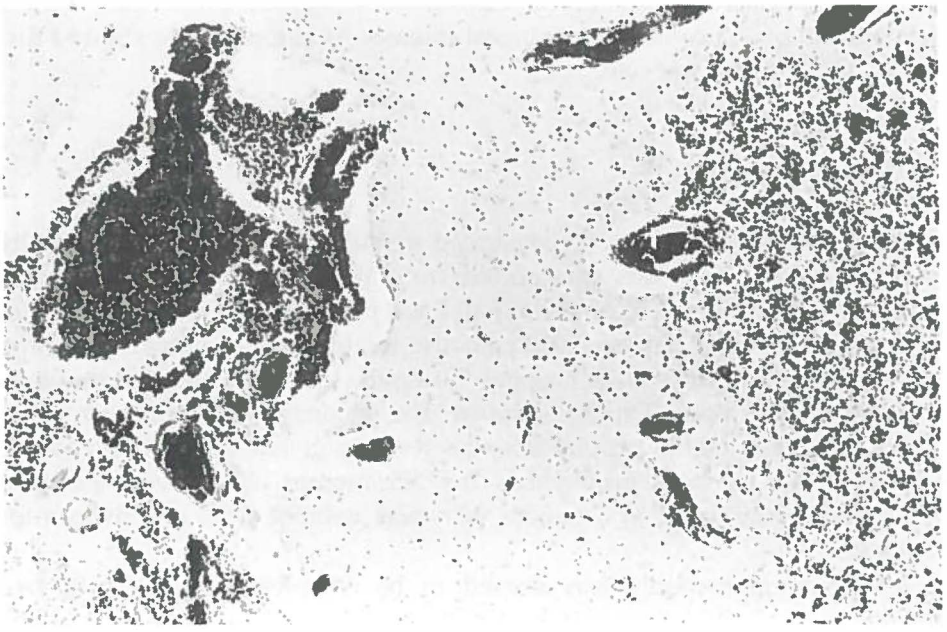

fig. 4: Grade 3 infiltration of the grey and white matter

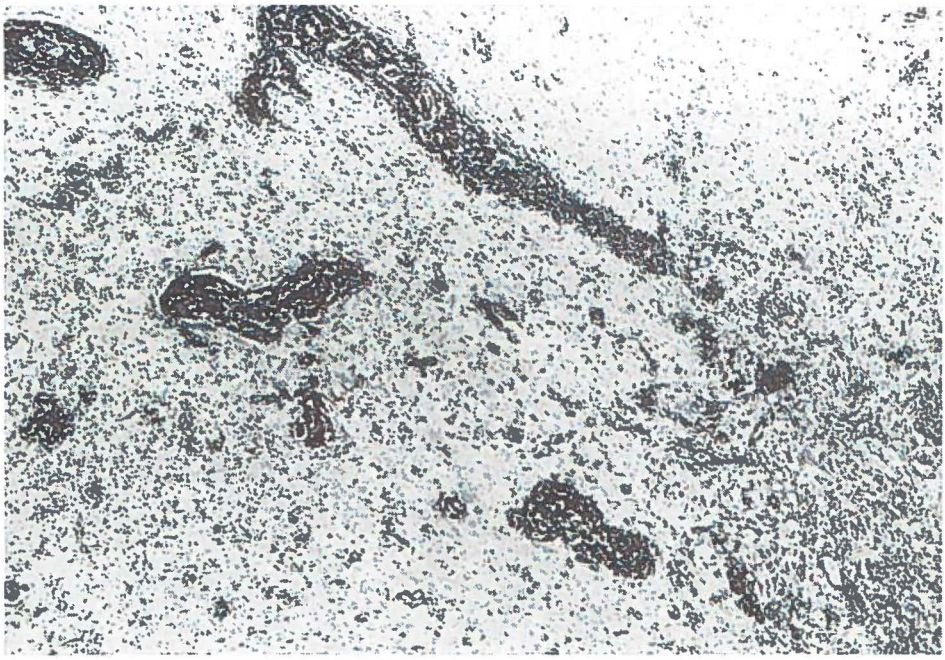

fig. 5: Grade 3 infiltration

Four patients died during complete remission or an aplastic phase. Two of these patients had been treated for meningeal disease. At autopsy none showed dissemination of malignant cells.

CNS prophylaxis

Meningeal involvement was demonstrated in four out of nine prophylactically treated patients. This was unexpected from the clinical situation in three patients, although it must be said that all these patients were in an end stage of their disease. Usually they received palliative treatment in an outpatient setting and they were admitted to the hospital during the terminal events. At that time CNS prophylaxis was often discontinued. The meningeal infiltration was mild in one patient to whom prophylaxis was recently given, and in two patients who had not received prophylaxis for 3-5 months. Extensive meningeal involvement was noted in a patient who was without CNS prophylaxis for 7 months.

Intraventricular prophylaxis proved to be completely succesful in five patients.

Table 1

	Sex	Age	Diagnosis	Disease duration (months)	Treatment modality	Time without treatment before death (months)	Clinical disease stage at time of death	Leukemia/ Lymphoma		Demye-lination	Additional findings
								CNS	extra-cranial		
1	f	39	c-ALL	12	Proph.	0	syst.relapse	-	++	-	
2	f	31	c-ALL	4	Proph.	0	CR	-	-	-	
3	f	36	c-ALL	32	Proph.,BMT	0	syst.relapse	-	++	-	
4	f	24	AML-M5	21	Proph.,BMT	6	CR	-	-	+ diffuse	focal necrosis
5	m	22	LBL	12	Proph.	4	NR	-	+++	-	
6	m	49	AML-M1	24	Proph.	3	syst.relapse	+	++	+ diffuse	CVA
7	f	64	c-ALL	24	Proph.	5	syst.relapse	+	++	+ diffuse	
8	m	37	AML-M2	10	Proph.	7	syst.relapse	+++	++	+ diffuse	CVA
9	m	42	T-LBL	11	Proph.	0	NR	+	+++	-	
10	f	51	T-ALL	40	Proph.,T	0	syst.relapse, ML	+	++	-	SDH
11	m	19	AML-M4	16	Proph.,T	3	syst.relapse, ML	+++	-	-	
12	m	23	c-ALL	17	Proph.,T	2	syst.relapse, ML	+++	+++	+ diffuse	
13	m	17	T-LBL	4	Proph.,T	0	aplasia	-	-	-	
14	f	38	AML-M5	12	T	2	syst.relapse,ML	+++	+++	focal	sec. to leukemia
15	m	58	LG NHL	10	T	2	CR	-	-	-	
16	m	60	IG NHL	17	T,RT cr.sp	0	NR, MenLy	+++	+++	+ diffuse	
17	f	24	T-IBL	85	T	0	syst.relapse	-	+++	-	
18	f	54	IBL	17	T,RT cr.sp	0	syst.relapse	-	-	-	
19	m	32	HG NHL	36	T,RT cr RT sp 2x	0	syst.relapse, MenLy	++	++	++ cerebral white matter	focal necrosis in cerebellum

For abbreviation of diagnoses: see chapters 2-4. BMT: bone marrow transplant, CR: complete remission, NR: non responder, Proph.: CNS prophylaxis, RT: radiotherapy, cr: cranial, sp: spinal, SDH: subdural hematoma, T: therapeutic regimen for ML or MenLy

Treatment of meningeal leukemia or lymphoma

Therapeutic regimens could be evaluated in 10 patients. Four patients were free of malignant infiltration of the CNS. One of these received low dose cranio-spinal radiation. CNS disease was present in six patients. The leukemic or lymphomatous infiltration of the CNS was limited to the arachnoid in one patient (grade 1), but was extensive throughout the meninges, brain and spinal cord in four (grade 3). One patient had an intermediate degree of dissemination (grade 2). The two patients with the lesser degrees of malignant cell dissemination had been treated untill death. Three of the four pateints with more extensive CNS disease had not received CNS treatment for a period of 2-3 months, and in another patient CNS treatment started just before death.

The subcutaneous reservoir and its catheter

Uncomplicated insertion caused minimal damage to the brain (fig.6). The example, which is shown stems from another more recent series. The area

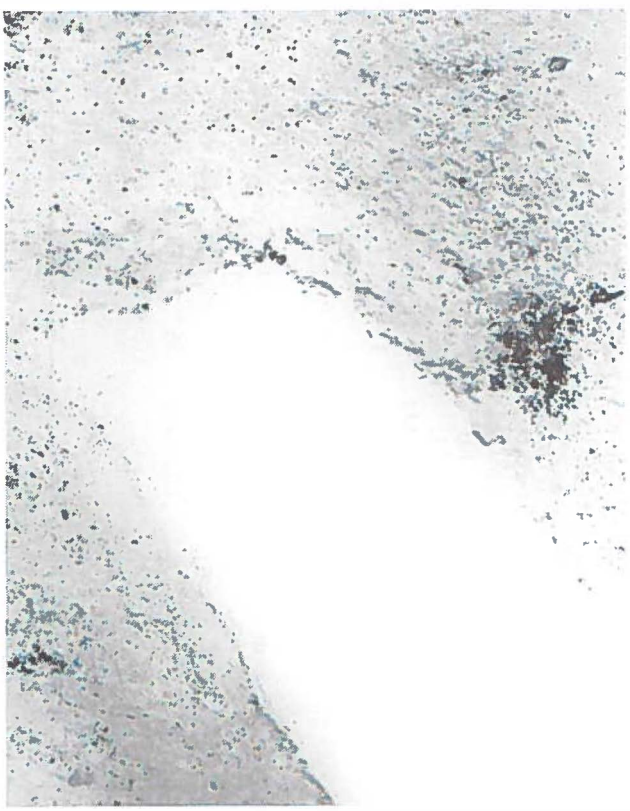

fig. 6:
Drain trajectory near the frontal horn of the lateral ventricle, 1 day after insertion

surrounding the drain between the Ommaya reservoir proper and the lateral ventricle did not show reactive changes, unless the patient had a history of technical complications with reinsertion of the drain. The initial drain trajectory was then identified by the presence of gemistocytes, macrophages and loosely structured gliosis. The total picture was one of repair.

Degenerative changes

Scanty demyelination of a diffuse nature was a feature of several postmortems of leukemia and lymphoma cases. This occurred in patients who had received very little CNS prophylaxis, as well as in patients treated with more intensive courses for meningeal dissemination. However, all patients got extensive systemic chemotherapy. This type of myelin degeneration was not related to the position of the drain or drain tip and can better be explained by cytotoxic effects of systematically administered drugs on the oligodendroglia.

Severe myelin breakdown was seen in two patients. In both cases this was already suspected during follow-up. One patient had a bone marrow transplant at another hospital and returned with toxic MTX levels in the CSF. Maximal dysfunction was attributed to lesions at the level of the spinal cord, cerebellum and brainstem. Autopsy revealed a necrotizing myeloencephalopathy, although this was not the cause of death. The other patient had received, over a period of 30 months, nearly continuous i.vt. treatment for cranial and spinal MenLy. In addition cranial radiotherapy was administered because of an intracerebellar NHL lesion and spinal radiation was given at two different levels for intradural and extradural tumor deposits. In this case loss of white matter fibers was seen in the centrum semiovale and corpus callosum. Secundary axonal degeneration, calcification and gliosis were also present. The cerebellar lesion showed liquefaction, but no tumor cells.

In these two patients toxic levels of MTX had been recognized during life and neurologic symptoms were attributed to damage caused by MTX. In the first patient this must be considered an iatrogenic accident. There was not much alternative in the second patient, since he needed to be treated and retreated time and again.

Conclusions

CNS Prophylaxis

From this analysis can be deduced that i.vt. chemotherapy can be sufficient in leukemia as well as in NHL, provided this is repeated and if necessary continued during systemic relapses.

Meningeal leukemia and lymphoma

The i.vt. treatment is capable of eradicating malignant cells in the meninges. When in the end stage i.vt. drugs are omitted, this is reflected in the occurrence of meningeal infiltration. The longer a patient with active systemic disease stays without i.vt. therapy, the more severe is the degree of meningeal dissemination.

Radiotherapy can have a beneficial effect too, but it is certainly not the ultimate cure.

Relationship between neurological assessment and neuropathologic findings

The early stage of meningeal disease does not lead to overt neurological symptoms. Detection is possible by CSF examination, but is hampered by deliberately omitting thorough neurologic evaluations in the terminal phase of the disease. Grade 2 and grade 3 dissemination were always discovered ante mortem.

Side effects

Implantation of an Ommaya reservoir has no great traumatic effect on the brain. A draintip can be repositioned and a plugged drain can be changed, without fear of causing neurological damage. This will leave behind a minimal scar.

Mild general neurotoxic effects are inherent to the systemically applied therapy. Intraventricular drug administration for CNS prophylaxis and CNS treatment will not cause parenchymal lesions unless toxic levels of MTX are maintained for a prolonged period.

References

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CHAPTER 7

THE OMMAYA RESERVOIR
Analysis of its feasibility

The implantation can be performed under local or under general anaesthesia. Experience of the neurosurgical staff as a whole and of every new staff member of the implantation team individually proved to be very important in minimizing the number of unsuccesful insertions. Most of the reservoirs requiring correction shortly after implantation were inserted when this experience was not sufficiently present. The maximum rate of reoperation in the initial phase was 10%. One of the early mistakes was a too long catheter, which led to malfunctioning, even when the draintip was still within the ventricular system. A position of the tip deep in the 3rd ventricle or near the aqueduct entrance can cause problems. Long catheters can also wander and penetrate the brain parenchyma. Shortening of the drain always resulted in normal functioning of the system afterwards. After gaining experience the need for reoperation has dropped to about 1% in more recent years.

Neurologic deficits were caused by the implantation of the device in two of the 126 patients, which formed the basis of this study. In both cases pyramidal tract signs and diplopia were found because of a rostral brainstem lesion. These signs were completely reversible after repositioning of the draintip.

Technical failures during follow-up were rare. Only two patients needed a new reservoir because of mere obstruction of the system without a malposition of the drain. Reservoirs can be used normally for many years, even as long as 11 years in our experience. Sometimes it can be difficult to draw large amounts (more than 5 ml) from the reservoir, most probably because of blockage by tissue of the choroid plexus. At such a moment unimpeded injection of sterile saline proves that it is still possible to push the choroid plexus away from the little holes in the drain, just as it is possible to suck it into the holes. Caution during subsequent CSF sampling will keep the system patent.

The first three months after insertion patients were on phenytoin to prevent epileptic fits. The dosage was reduced over two more months. This prevention was completely successful.

Another preventive measure at the time of implantation was the prescription of an antibiotic. Cotrimoxazol was given for three days, beginning the evening before the operation.

Fourteen episodes of infection of the meninges and ependym were seen in 13 of the 126 patients. In two cases this occurred spontaneously at a time of severe

leukopenia. Two postoperative infections were seen. The other cases were related to handling of the reservoir. The domes were punctured for CSF examination and/or drug instillation more than 1500 times. Quite often hastiness of the doctor or improper preparation of the injection area could be traced as causative factors. The infection was in three cases asymptomatic and in two of these an accidental finding. The other patients had always very few signs and symptoms, e.g. headache or mild nucheal rigidity. Focal signs were never seen. Infections were caused by bacteria from the permanent skin flora. With i.vt. and i.v. cefradine or cefuroxim the meningitis could be cured in all 13 patients. One reservoir remained contaminated although the patient had no complaints. This reservoir was removed and after 10 days of antibiotics a new one was inserted without any further problems.

Our experiences taught us that aseptic handling is very important in preventing infection at the time of puncturing the dome of the reservoir. Since more stringent measures became standard procedure, infections are exceptional. These measures include: preparation of the skin with chlorhexidin 0,5% solution for 10 minutes, the use of sterile adhesive drapings over the surrounding skin and sterile drapings in the working area, the use of a 25 gauze infusion set with a butterfly needle, which creates the possibility to change syringes at some distance from the skin.

After CNS prophylaxis neither focal nor diffuse leukoencephalopathy was seen. Two cases of diffuse leukoencephalopathy occurred after cranial radiotherapy and respectively, 3 years of i.vt chemotherapy, and toxic MTX levels following a bone marrow transplantation procedure.

All patients preferred the nearly painless injections in the reservoir to spinal taps. In their daily life they were not bothered by the device, neither were they prevented from sporting. Patients who objected after a certain time to the use of the reservoir also refused other parts of their therapy at that time. Their attitude was not related with the presence or the use of the subcutaneous device, but could be explained by the inability to cope with their disease progression any longer.

In conclusion it can be said that the Ommaya reservoir can make a substantial contribution to the management of the CNS problems in patients with hematopoietic malignancies because

1. technical imperfections will be infrequent when the neurosurgeon is dedicated and experienced,
2. infection prevention lowers the complication rate in such a way that the Ommaya reservoir is a safe device to use, and
3. patient's acceptance is very good.

CHAPTER 8

DISCUSSION

Evaluation of the results of i.vt. CNS prophylaxis

Despite CNS prophylaxis a primary CNS relapse developed in 5.6% of the ALL, in none of the AML patients and in 3.7% of the NHL group. A marginal note for the ALL patients was that in both cases the routine CNS protocol was violated.

All other cases of ML and MenLy were linked with systemic relapses. In AML this was seen in 7%. Such occurrence in ALL and NHL was respectively 8.3% and 22.2%.

If a BM/systemic relapse occurs, the meninges are reseeded, negating the effect of any prior CNS therapy. It would be better to consider only a meningeal relapse without a systemic relapse within 30, preferably 60 days a failure of preventive therapy.

Ventricular CSF cytology reflects in our experience the situation in the lumbar CSF to a high degree. Only rarely did a negative cytology at the level of the ventricles necessitate a lumbar puncture in a patient with clinical suspicion of meningeal involvement.

The available neuropathological material confirmed the notion that the longer a patient with active acute leukemia or NHL remains without CNS prophylaxis, the more the meninges are seeded with malignant cells. No untoward side-effects of the CNS prophylaxis were seen in the brain.

ALL

The incidence of primary CNS relapse in ALL compares well with the results of CNS prophylaxis in other series of adult patients. In these studies patients received either the conventional* prophylaxis (incidences of 0, 3.2, 10.7% respectively)[1-3] or i.t. prophylaxis. The latter either for a short period (incidence: 11.1%)[4] or on a long term schedule of 2-3 years (incidence: 4.3%).[2] The best results were obtained with i.t. prophylaxis, which was changed to i.vt. in patients with an initial WBC over 20 x 10^9/l, and which was maintained for 3 years (incidence: 2.8%).[5]

Recently a long term follow-up study in children with ALL showed that i.t. CNS prophylaxis over a period of 3 weeks after achieving CR was insufficient in preventing primary CNS relapses. Such an event occurred in 36% of these

* Cranial radiation (2400 rad) and i.t. MTX (5-6 times in 2,5-3 weeks)

patients. However the ultimate disease free survival in this patient group was not different from those that received cranial radiation and identical i.t. treatment, or craniospinal radiation. Those patients suffered more often other initial events or death in remission.[6]

From these unfavorable results of i.t. prophylaxis may not be concluded that prophylaxis with the exclusive use of drugs is inferior. An important factor may be the duration of this treatment.

The optimal duration is not known. Important in solving this matter is, whether there exists a difference between adults and children regarding the CNS problem. When that is not the case conclusions from trials in one group can be used to formulate strategies for the other.

To start with this last question, it is of interest to note that indeed the MSKCC protocol L2, identical for children and adults except for the duration of CNS prophylaxis (children 3 years, adults 2 months) had different rates of primary CNS relapses, respectively 5.5 and 11%.[4] When in a later protocol L10–10M the schedule was similar the difference disappeared (resp. 1.8 and 2.8%).[7,5] This provides enough support to use the evidence vice versa.

In favor of an i.t. maintenance of 120 weeks are the results from a trial in standard risk ALL children. This compared three groups: 1. rotating drug pairs in combination with cranial radiation (1800 rad), initial i.t. MTX 12 mg/m^2 five times in 2,5 weeks followed by i.t. MTX every 12 weeks for 120 weeks; 2. i.v. MTX 1 g/m^2 and i.t. MTX (12 mg/m^2) weekly for three times followed by the same i.t. schedule as in the first group together with i.v. MTX every 6 weeks and 3. historical controls. The initial CNS relapse rate was essentially the same.[8] In another study low risk ALL children on the drug only arm had similar CNS relapse rates on i.t. maintenance schedules of 2 and 3 years.[9]

Altogether the choice of a maintenance length of 2 or 3 years seems made arbitrarily.

Our results have demonstrated that in ALL i.vt. CNS prophylaxis during a limited period of nearly half a year suffice. Because there is no neurotoxicity attached, the opportunity is created to repeat the prophylaxis courses easily. Since adults tend to have more systemic relapses than children, this will be valuable. Although the succesful prevention of ML may not have a useful impact on long term survival, nevertheless the quality of life is so much better without meningeal disease, that it is difficult to argue against a convenient and non-neurotoxic preventive measure.

In the meantime frequent CSF control during systemic remission and in the early phase of a systemic relapse can be performed without hindrances. This offers a better insight in the real incidence of meningeal leukemia. It is striking how insufficiently documented incidence data in the literature often are.

AML

In ALL CNS prophylaxis is considered mandatory, but how about AML?

In chapter 3 some of the main points leading to controversial opinions are outlined. Autopsy material from before 1975 showed a similar rate of meningeal involvement as in ALL.[10] Yet this did not convince enough as long as the survival of these patients was generally short, because the evidence did not surface. The matter stayed controversial. When active detection was pursued, initial CNS involvement tended to be rather frequent (20.7%).[11] With the same approach ML was detected during CR in 16%.[12] When CNS prophylaxis is used, most CNS relapses occur concurrently with BM relapses.[13] From these facts can be deduced that the tendency to infiltrate the meninges certainly applies to all stages of AML and not only to the uncontrolled disease process. Acute leukemia patients with monocytoid features (M4 and M5 subtypes) are more at risk for meningeal involvement.[12,14] Especially among M4 patients abnormalities of chromosome 16 were associated with meningeal and also intracerebral disease.[15]

It is not unthinkable that in later years the introduction of AraC in the systemic treatment may have changed the number of CNS manifestations.

CNS prophylaxis with intermittent maintenance i.t. MTX was able to diminish the incidence of ML.[11] If on the contrary from the 8th AML trial of the MRC is concluded that CNS prophylaxis with i.t. MTX or AraC is not warranted, because primary CNS relapses were even more frequent in the patients with than in those without prophylaxis, one overlooks the fact that the prophylaxis lasted only 3 weeks.[16] Such a short period is insufficient to eradicate the slowly proliferative leukemic cells in the CSF/CNS. Ambiguity speaks also from this trial design as CNS prophylaxis for patients less than 13 years old is taken for granted, but those between 13 and 55 year are randomized and the elderly receive none.

Although in AML adequate CNS prophylaxis can effectively prevent ML, this approach has not prolonged systemic remission.[17] Our results in AML patients may suggest a positive influence of CNS prophylaxis on the length of 1st BM remission duration and on survival, but statistical significance was not reached. Even if that is the case and permanent cure is not within reach, the purpose of therapy will be to prolong the disease free survival. This reflects the combined effect of all events, isolated CNS relapses, initial BM relapses, initial relapses at other sites and CNS relapses combined with other relapses. With inadequate courses of prophylaxis a preponderance of CNS events can be expected, whereas with more succesful employment of CNS prophylaxis the lesser number of CNS relapses will be offset by the other forms of relapse. CNS relapse can be seen as an early harbinger of more widespread disease and an indicator of an increased likelihood of future relapses at other sites.

So essentially a choice has to be made between eradication of CNS dissemination initially and at the time of systemic relapses, or more agressive treatment of systemic disease, meanwhile hoping for the best for the elimination of malignant cells in the meninges and awaiting what comes on first. Crucial to this problem is whether one considers the manifestations of meningeal disease, more precisely specified as multiple cranial neuropathy, cauda equina dysfunction and high intracranial pressure, more or less menacing for the quality of life than symptoms due to BM invasion, and also which set of signs and symptoms is more easy to treat, once it has developed.

CNS prophylaxis seems warranted for these AML patients who are the most at risk, namely the M4 and M5 subtypes.

In view of the above, reiteration can be considered mandatory. This eliminates the use of radiotherapy. One possibility could be high dose systemic therapy (e.g. AraC, VP16), but toxic side effects are inherent to this modality. The advantages of i.vt. over i.t. administration have been discussed previously. Side effects of i.vt. AraC are negligible. An early start, i.e. immediately after reaching CR can be advocated. From our experience can be concluded that in AML (M4, M5) an i.vt. course every 4 weeks with a duration of 5.5 months is enough for adequate protection.

NHL

At first CNS prophylaxis in NHL was not considered at all. Gradually meningeal (and intracerebral) dissemination was (were) recognized as a problem. The confusing nomenclature and the hodgepodge of patient groups evaluated as if they were a homogeneity, did not promote the insight. The question whether NHL patients need CNS prophylaxis at all, can be better posed as: Which subgroups of NHL will benefit from CNS prophylaxis? Consensus has been reached that lymphoblastic lymphoma (LBL) carries a high risk of CNS involvement, as does NHL with BM involvement or extranodal disease.[18,19] The idea that (some forms of) diffuse histology (Rappaport classification) may benefit, is more difficult to transpose in such a way that it fits the Kiel classification.

The NHL literature also seems to reflect the same artificial dichotomy between children and adults as with the leukemias. Age <35 years was identified as a risk factor, but LBL is more frequent in the younger age group.[19,20] It is probably not so much age that dictates prophylaxis as the histological type of NHL.

Epidural disease is a subject per se. From a neuroanatomical point of view it has wrongly been counted under CNS disease.[21,22] On the other hand it forms a risk factor for leptomeningeal invasion and patients with this localization should qualify for prophylaxis.[23,24]

How to institute CNS prophylaxis for high grade malignant NHL is guided by the same principles as in acute leukemia. When at the one hand it is shown that cranial radiotherapy is not mandatory for a good CNS prophylaxis in children with NHL[24] and at the other hand the younger age group has more unfavorable histologies, this seems to settle the question which modality one should prefer.

Surely the question should be addressed, whether with the use of the i.vt. method the same drug regimen is effective as in the leukemias.

Not much is known about the duration of a prophylactical course either. Only a few studies, some with a limited number of patients are published. From these can be deduced: that a late start (week 7) is not successful in preventing CNS relapses,[25] further that very short i.t. courses either with MTX or with AraC were disappointing,[26,27] that long term i.t. courses with a relatively low frequency of MTX administration were insufficient,[28] that the "conventional" form was adequate,[29] but that long term i.t. MTX every 4 or 8 weeks was just as good.[30,31] Others believe that intensive i.v. combination chemotherapy which includes HD-MTX and/or AraC may be all that is necessary.[32,23] How reliable this is, is difficult to judge since in the first study T-cell LBL and Burkitt lymphoma were excluded.

In what way can our material presented in chapter 4 contribute to these issues?

In the majority of the patients MenLy developed during active disease and well within a short time of presentation or systemic relapse (median 2 months). This means that propylaxis should be instituted early, especially in LBL. A deviation in the prophylaxis in LBL patients was shortly followed by the development of MenLy. As a matter of fact MenLy evolved so often during treatment and palliation for LBL that a more intensive preventive regimen is indicated, either i.vt. or systemic. Because of the small numbers in the other subgroups no definite conclusions can be made, but the impression exists that IBL and polymorph CBL irrespective of BM status may benefit from CNS prophylaxis. Initial BM involvement in the intermediate grade NHL was frequently (100%) seen in those who developed MenLy. It remains to be seen if this forms an indication for CNS prophylaxis. Patients with epidural disease who received prophylaxis were adequately protected. So we agree with the opinion to offer them prophylaxis as well.

Having tried to define the patient groups who may need prophylaxis, and the time preventive treatment should start, it is necessary to consider the duration of this treatment. The setting of the development of meningeal dissemination in lymphoma is somewhat different from that in leukemia. In leukemia the CNS can be seen as a pharmacological sanctuary, but that is not the major critical issue in NHL. Here mostly loss of systemic disease control and/or poor response to initial treatment precede the meningeal dissemination. Conse-

quently CNS prophylaxis in NHL should consist of two components. During early remission prophylaxis has to be focused on the prevention of primary CNS relapses. Our results indicate that with i.vt. prophylaxis this part is effectively approached. The other part will best be covered by better systemic disease control. As long as that is not available a continuous CNS prophylaxis will be indicated when no systemic remission can be obtained, because once MenLy has developed it is hard to suppress.

Evaluation of the results of therapy for ML in ALL and AML and for MenLy in NHL

On i.vt. treatment a complete CNS remission was readily obtained in the leukemia patients, but this was more difficult in NHL. In the last group an acceptable improvement or stabilization of the symptoms was reached in 73%, but less than half of the patients met the criteria for complete CNS response.

Median survival from the time of diagnosis of meningeal disease was respectively 7 months in ALL, 5 months in AML and 3 months in NHL. Symptomatic patients did worse than asymptomatic. Those who had received prior CNS prophylaxis, had also longer survival periods after the ML/MenLy diagnosis was made. However none of these differences was statistically significant.

Meningeal Leukemia

CNS remission lasted till death or till the end date of the study evaluation in 45% of the evaluable ALL and 67% of the AML patients. In those AML patients who experienced a recurrence in the CNS, it concerned always an asymptomatic terminal event.

One third of the CNS recurrences in ALL patients was asymptomatic. Two third of these patients achieved a second CNS remission and in half of them this persisted till death. Three of four terminal events were symptomatic.

Radiotherapy for uncontrollable ML was used in two cases of ALL in the end stage.

Meningeal dissemination was never the cause of death neither in ALL, nor in AML. Although this means that the treatment schedule was effective in containing the morbidity of meningeal dissemination in AML as well as in ALL, and also that the ML treatment regimen was satisfying for AML patients, a more intensive therapy for the ML cases with ALL may be fruitful in preventing the number of CNS recurrences.

The following concepts are conceivable: 1. induction of CNS remission by HD-MTX or HD-AraC i.v. and maitenance i.vt. therapy for longer than half a

year; 2. CNS remission induction by i.vt. treatment and maintenance with intermittent low dose craniospinal radiotherapy in conjunction with i.vt. MTX at regular intervals, till a certain maximum total dose; 3. the same induction, consolidated by limited craniospinal radiation and maintained with intermittent i.vt. drugs; 4. an i.vt. dosage regimen based on the C x T principle; 5. the use of i.vt. triple drug therapy.[33-38] The first option has considerable toxicity and the question is how effective it can be in eradicating or suppressing leukemic cells previously exposed to chemotherapy. Facts associated with the fifth possibility are discussed below. As a disadvantage of the fourth method counts that it is difficult to apply on an outpatient basis. The other two methods merit to be evaluated.

Meningeal Lymphoma

A permanent cure of MenLy was seen in 40% of the complete CNS responders. Only one patient is a long term disease free survivor. Recurrences in the CNS in NHL had quite often a protracted course. In NHL it was several times (in 33%) necessary to resort to radiotherapy either cranial or in the region of the cauda equina to treat MenLy. Of course dural and intra-axial localizations received RT as well.

The relatively short survival after the diagnosis MenLy was made, was in the same range as in other studies. Most of them used a combination of i.t. or i.vt. MTX and cranial radiation[23,39,40] or only i.t. treatment.[18] Survival in these NHL patients does not only depend on CNS disease, but to a great extent on systemic manifestations. To prolong survival means to find better treatment for both. In the meantime morbidity of MenLy has to be forced back. Whether this will originate in more intensive i.vt. drug treatment or in the use of radiotherapy, or in both can not be said on the moment and further investigations are needed. The method of i.vt. MTX, and if necessary AraC (first intensive, later maitenance), together with radiotherapy to focal area(s) of involvement seems attractive in the light of a good response rate and few recurrences.[41]

The efficacy of the drugs available for treatment of the CNS in leukemia and non-Hodgkin's lymphoma

In this study two drugs, MTX and AraC, were administered into the ventricular CSF. The drugs were always given separately. Their effectiveness is determined by the concentration reached in the whole CSF compartment and by the time of exposure to therapeutic concentrations.

However there is no conclusive agreement on the "therapeutic" level of MTX or AraC. For both highest and lowest suggested levels are a factor 100 apart.

Estimations for MTX vary from 10^{-6} to 10^{-8} M/l, and for AraC the suggested levels are between 4×10^{-7} and 4×10^{-5} M/l.[42-45]

Another uncertainty is to what extent i.v. administered drug influences the CSF pharmacokinetics. The CSF/serum ratio for MTX is given as 0.01-0.03 in patients with an intact blood brain barrier and 0.157 in patients with meningeal leukemia.[42,46-47] Variable is the CSF/serum ratio given for AraC: 0.06-0.60.[45,48] Here a distinction between patients with and without meningeal involvement was not made.

For reliable results not only the dosage is important, but also the distribution in the CSF and the way of elimination from the CSF.

Elimination of drugs from the CSF has been shown to be mainly by CSF bulk flow and resorption, and to a variable degree by diffusion into neural tissue and uptake by capillaries. The minimum rate is established by the CSF bulk flow. The maximum rate of drug washout is only seven times the minimum rate. For MTX elimination the contribution of diffusion into tissue is only small.[49,50]

When lumbar i.t. injections with MTX are given in close succession, the elimination is slow for the first two injections and much faster for the following injections thereafter. This last pattern does not result in adequate CSF levels, but the slow pattern maintains a CSF level of 5×10^{-7} M/l for 18 hours. The slow pattern is restored after a free interval of i.t. drug administration. These concentrations are calculated for the lumbar level, but it is questionable how far this applies at the cranial level, where drug distribution can be very unpredictable. Comparison of the levels to be expected after i.vt. injections with those after lumbar i.t. injections can only be superficial. The elimination process will probably be subjected to the same factors. Distribution will be different. Distribution after i.vt. injections is good, as has been described earlier and as can be concluded from our CSF flow study. In contrast lumbar i.t. injections are hampered by dural leakage, and concentrations reached at the cranial level are insufficient when the usual small volumes are injected.

Probably as a consequence of the above mentioned facts, stated half life times of MTX in the CSF differ considerably. In children they are either of the slow type: 4.5 h. and 14 h. (biphasic) or of the fast type: 1 h.[50-52] In adults half life is 9 h. and in the elderly often even longer.

The half life time of AraC in CSF is 1 h 20 min- 2h 20 min, which is much longer than in plasma., because of the lack of deaminase activity in the CSF.[44,45]

It is not surprising that because of all these uncertain factors the prophylactic and the therapeutic schedules are often based on empirical grounds and much less on pharmacokinetics derived facts. Just as it was found that in young children the i.t. MTX dose could be better calculated according to age than to body surface area, so is it necessary to lower the MTX dose in the elderly (>60 year) and in those with extensive meningeal involvement during initial therapy. The AraC dose however can always remain the same in all adult categories.

Placing an effective chemotherapeutic agent into the ventricles doesn't assure its widespread distribution through the neuraxis in all patients with meningeal disease. More information about the potential drug distribution in these patients can be derived from scintiventriculography prior to the initiation of i.vt. treatment. This may very well influence the patients individual treatment schedule. Radiopharmaceutical follow-up studies may form an indispensable prerequisite to the study of alterations in pathologic conditions.

How can be made use of the available drugs more effectively? When meningeal disease in ALL/NHL reacted poorly to MTX, it was often possible to score better results by using AraC. Does this mean that alternating MTX and AraC is advisable? Although this method is professed in some studies a rational support is not stated.[36,53] It is suggested that AraC preceding MTX 1-72 h. may have synergistic action.[54]

Simultaneous use of MTX, AraC and hydrocortisone (HC) is also advocated. The idea for adding HC is that it may act oncolytic and that it prevents chemical meningitis. However with i.vt. therapy this forms no real problem, and furthermore the injectable preparation contains chemicals that can cause inflammatory reactions on their own.[55]

After triple i.t. injection HC and AraC do not seem to influence the CSF level of MTX, but HC inhibits MTX accumulation in L1210 leukemic cells.[56,57] HC as well as prednisone decrease the effect of MTX on L1210 and human leukemic cells, but dexamethasone and prednisolone have no such effect.[58] The CSF/plasma ratio of dexamethasone is higher than for prednisolone, because of a difference in protein binding in plasma.[59] Dexamethasone is effective for cerebral edema surrounding metastases and tumors and under its influence primary cerebral lymphoma may vanish for a considerable period of time. Concerning the controversy around the use of corticosteroids it may be concluded that i.t./i.vt. HC is not needed for the elimination of ML/MenLy, and that oral dexamethasone may be more valuable than prednisolone.

CONCLUSION

In closing the answers to the questions formulated in chapter 1.9 can be given. In these answers one should read for AML : M4 and M5 subtypes and for NHL : high grade malignant NHL.

Question 1. Is CNS prophylaxis with i.vt. chemotherapy at least as good as the "generally accepted standard" method?

Answer The results of i.vt. CNS prophylaxis during half a year in adult ALL patients equal the results of the "generally accepted standard" method. In AML, in initial episodes of NHL and during systemic relapses of most types of NHL the outcome is also adequate.

Question 2. Can this form of CNS prophylaxis repeatedly be applied?

Answer This form of CNS prophylaxis can be reiterated, more than once, in patients who experience a systemic relapse.

Question 3. Is this treatment modality acceptable as preventive measure in relation to its neurotoxicity and its complication rate?

Answer Side effects of the drug treatment are few. Long-term neurotoxicity was not seen with i.vt. CNS prophylaxis. Iatrogenic introduced infection can be avoided with strict aseptic procedures when using the reservoir. Neurosurgical expertise is important for minimizing insertion difficulties and possibly subsequent drain obstructions. Provided these two criteria are fulfilled the complication rate is low.

Question 4. How effective is i.vt. chemoterapy for meningeal involvement?

Answer ML can be treated via an Ommaya reservoir with good results. The neurologic morbidity can be contained till the end of life. However when the same dosage and frequency were used, the employed drugs did not always succeed in suppressing the meningeal involvement in NHL.

Question 5. Is this method convenient for the patient?

Answer Patients consider the indwelling reservoir no hindrance in their day to day life and prefer the use of the reservoir over multiple spinal taps.

Question 6. Are there any problems attached to this treatment modality which need to be addressed in the future?

Answer When systemic disease cannot sufficiently be controlled in LBL, CNS prophylaxis should probably be given according to a more intensive regimen. This fact needs further attention.
For MenLy a combination treatment of more than one drug and (focal) radiotherapy must be investigated.

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SUMMARY

This thesis deals with the CNS involvement in some hematopoietic malignancies such as ALL, AML and high grade malignant NHL. The study concerns adult patients. Attention is focused upon prevention of this complication and also upon the treatment possibilities, once dissemination has occurred.

For better understanding an overview of historic facts, pathogenesis and subsequent clinical findings is given in the first chapter. Early meningeal dissemination can go undetected, certainly if no thorough surveillance of the CSF is undertaken. The difficulties in diagnosing ML and MenLy, the options available for CNS prophylaxis and treatment of meningeal disease along with the attached neurotoxicities are described. On the basis of these facts i.vt. chemotherapy administered through an Ommaya reservoir was chosen as CNS prophylaxis. The same approach, but with a different schedule was used for the treatment of ML and MenLy. To evaluate these procedures several questions were formulated.

To answer these questions patient data from a 10 year period were analyzed. This comprises also the early experiences. The clinical data pertinent to the preventive regimen and the therapeutic schedule in ALL, AML, and NHL are presented in three consecutive chapters.

A study of the normal CSF flow after introduction of a radiopharmaceutical through an Ommaya reservoir into one of the lateral ventricles is the subject of chapter 5. Distribution is excellent throughout the cerebral ventricles and the cranial and spinal subarachnoid space. Sufficient drug distribution can be expected in the mild forms of meningeal dissemination, but further scintiventriculographic investigations are needed to delineate the degree of meningeal disease that becomes too severe to be treated solely by i.vt. drugs.

Neuropathologic data of a limited number of patients were available and are reviewed in chapter 6. These data emphasize the usefulness of i.vt. CNS prophylaxis and the i.vt. treatment of ML and MenLy. It seems a fair conclusion that this form of i.vt. prophylaxis is not neurotoxic. More frequent i.vt. chemotherapeutic drug administration gave only rise to sequelae, when MTX levels in the CSF had been in the toxic range for a considerable period of time.

Special attention was payed to possible complications of the Ommaya reservoir proper and to the opinion of the patients on the insertion and the use of the device. These facts are presented in chapter 7. Patients acceptance was very good and they stated preference for the nearly painless injections in the reservoir to lumbar punctures. Provided infection prevention gets careful attention every time the Ommaya reservoir is used, either for diagnostic purposes or for drug administration, the risk of iatrogenic infections is low. Inadvertent infections of the reservoir, the ependym and the meninges can be cured without

the need to remove the device. The number of insertion imperfections depends for a great deal on the expertise of the neurosurgical staff members. Malfunctioning of the reservoir cannula independent from the implantation procedure is rare.

In chapter 8 the outcome in the different series is discussed, also in relation to more recent literature references. From these results, the findings of the CSF flow study, the neuropathologic evaluation and the feasibility analysis the answers to the evaluative questions were formulated.

The following paragraphs are a compilation of the answers to some of these questions and the consequences for the different patient groups, resulting from these answers.

CNS prophylaxis by way of an Ommaya reservoir is advocated for adult patients with ALL and AML (M4 and M5) after attaining CR. A systemic relapse forms an indication to resume the prophylaxis.

In NHL the same holds true for LBL, IBL and polymorph CBL with BM involvement (or possibly irrespective of BM involvement) and in the case of initial epidural deposits; in these NHL patients the prophylaxis should begin when the tumor responds favorably to systemic treatment. An early start of CNS prophylaxis is especially important in LBL. The prophylaxis must be repeated in the NHL patients as soon as a systemic relapse occurs.

More investigations are needed to find a better prophylactic schedule during relapses of LBL.

ML can be cured or controlled by i.vt. therapy.

With similar treatment for MenLy difficulties are encountered which suggest that a study concerning a more intensive treatment regimen in conjunction with radiotherapy merits consideration.

SAMENVATTING

De uitzaaiingen naar het centrale zenuwstelsel (CZS) welke kunnen optreden bij hematopoietische maligniteiten, zoals ALL, AML en NHL met een hoge maligniteitsgraad, worden in dit proefschrift besproken. Het patientenbestand beperkt zich tot volwassenen. De aandacht wordt enerzijds gericht op het voorkomen van de meningeale disseminatie, anderzijds op de behandeling ervan wanneer deze toch heeft plaats gevonden.

Om een beter inzicht te krijgen in de problematiek wordt eerst een overzicht gegeven van enkele historische gegevens, de pathogenese en de eventueel daaruit voortvloeiende klinische verschijningsvormen. In hoofdstuk 1 wordt verder ingegaan op de moeilijkheden, die zich kunnen voordoen bij het stellen van de diagnoses meningeale leukemie (ML) en meningeaal lymfoom (MenLy). Meningeale uitzaaiing wordt in de beginfase niet opgemerkt, tenzij de liquor zeer frequent en nauwlettend wordt onderzocht. Voorts komen aan bod de verschillende opties, die er zijn voor CZS profylaxe en de behandeling van meningeale disseminatie, benevens de hiermee verbonden neurotoxische verschijnselen. Op grond van deze feiten werd gekozen voor een CZS profylaxe uitsluitend bestaande uit chemotherapie, welke intraventriculair (i.vt.) via een Ommaya reservoir werd toegediend. Dezelfde benadering werd gebruikt bij de behandeling van de meningeale uitbreiding van leukemie en lymfoom, zij het dat het doseringsschema anders was. Om de resultaten van deze handelwijzen te evalueren werden enkele vragen geformuleerd.

Ten einde deze vragen te kunnen beantwoorden, werden de gegevens van patienten behandeld tussen 1976 en 1986 geanalyseerd. Hierin zijn ook de allereerste ervaringen verwerkt. In drie achtereenvolgende hoofdstukken worden de klinische gegevens, die betrekking hebben op de preventie en op de behandeling van CZS disseminatie bij respectievelijk ALL, AML en NHL besproken.

De normale liquor-circulatie vanuit de zijventrikel werd onderzocht middels injectie van een radiofarmacon in het Ommaya reservoir. Dit wordt beschreven in hoofdstuk 5. Het bleek dat de verspreiding in het gehele ventrikelsysteem en de subarachnoidale ruimte, zowel craniaal als spinaal, uitstekend is. Te verwachten valt ook dat bij lichte vormen van meningeale disseminatie de verspreiding van i.vt. geinjiceerde medicamenten voldoende zal zijn. Met scintiventriculografie zal nagegaan moeten worden wanneer een meningeale aandoening zo uitgebreid is geworden, dat het irreëel is te veronderstellen dat i.vt. therapie alleen, curatief zal zijn.

Bij een beperkt aantal patienten was obductie van het CZS verricht. De gegevens zijn verwerkt in hoofdstuk 6 en tonen aan dat deze CZS profylaxe het beoogde doel bereikt, terwijl ook bij ML en MenLy de i.vt. behandeling zijn vruchten afwerpt. Het lijkt alleszins redelijk te concluderen dat de gevolgde

vorm van CZS profylaxe niet neurotoxisch is. Bij meer intensieve i.vt. therapie werden slechts afwijkingen waargenomen wanneer de MTX spiegel in de liquor gedurende langere tijd te hoog was geweest.

In hoofdstuk 7 is speciale aandacht besteed aan de mogelijke komplikaties verbonden aan het gebruik van het Ommaya reservoir zelf. Tevens werden de opvattingen van de patienten dienaangaande weergegeven. De implantatie procedure en de aanwezigheid van het reservoir werden zonder problemen geaccepteerd, temeer daar het vrijwel pijnloze aanprikken van het reservoir verre verkozen werd boven een lumbale punctie. De kans op iatrogene infecties is laag, mits infectie preventie zorgvuldige aandacht krijgt, telkenmale wanneer het Ommaya reservoir gebruikt wordt, of dit nu om diagnostische redenen is, dan wel om medicijnen te injiceren. Onverhoopte infecties van het reservoir, het ependym en de meningen kunnen succesvol behandeld worden zonder dat het reservoir verwijderd behoeft te worden. Hoe groter de expertise van de neurochirurg is, des te minder onvolkomenheden, voortkomend uit het inbrengen van het reservoir, zullen optreden. Dat de ventriculaire catheter op een later tijdstip slecht zal blijken te functioneren komt uiterst zelden voor.

De resultaten binnen de verschillende patienten series worden op een rij gezet in hoofdstuk 8 en vergeleken met recente literatuur gegevens. De hieruit voortvloeiende conclusies, de bevindingen van de liquor-circulatie studie, de neuropathologische evaluatie en de analyse van de bruikbaarheid van het Ommaya reservoir leverden de antwoorden op de vragen, die gesteld waren om de gevolgde werkwijzen te evalueren.

In de volgende alinea's zijn de antwoorden op sommige van die vragen en de gevolgen daarvan voor de verschillende patienten categorieën samengebracht.

CZS profylaxe middels een Ommaya reservoir wordt aanbevolen voor volwassen patienten met ALL en AML (M4 en M5) na het bereiken van een complete systemische remissie. Bij een systemisch recidief dient de profylaxe hervat te worden.

Ditzelfde geldt voor NHL bij LBL, IBL en polymorf CBL met beenmerg invasie (of misschien ook wel ongeacht de beenmerg status) en bij die gevallen waar initieel epidurale uitbreiding aanwezig is; bij al deze patienten moet de profylaxe aanvangen wanneer de tumor goed reageert op de cytostatische behandeling. Vooral bij LBL is een vroeg begin van CZS profylaxe belangrijk. Herhaling van de profylaxe is geindiceerd als een systemisch recidief wordt aangetoond.

Verder onderzoek is nodig naar een betere profylaxe tijdens recidieven van LBL.

ML kan met i.vt. therapie tot verdwijnen worden gebracht of goed onder controle gehouden worden.

Bij een overeenkomstige behandeling van MenLy worden echter moeilijkheden geconstateerd, die suggereren dat hierbij een studie naar een meer intensief behandelingsprotocol, waarvan ook radiotherapie deel uit kan maken, aanbevelenswaardig is.

TERUGBLIK

Doordat Prof.dr. H.O. Nieweg zo'n oog had voor de bijzonder invaliderende neurologische complicaties van ALL en mij suggereerde dat daaraan maar eens iets gedaan moest worden, was de basis voor de beschreven behandelingsvorm gelegd.

De opeenvolgende stafleden van de afdeling Hematologie hebben ieder op geheel eigen wijze bijgedragen aan het denken over en het uitvoeren van CZS profylaxe en behandeling. Gedurende het op schrift stellen van onze gemeenschappelijke ervaringen was de samenwerking het meest intensief met mijn medeauteurs Simon Daenen en Gustaaf van Imhoff. Tegelijkertijd vormde Ruud Halie als promotor een bemoedigend en optimistisch klankbord. Dit maakte dat de gehele schrijfperiode plezierig bleef. Zonder de inzet van de verpleegkundigen, de registratieassistenten en de maatschappelijk werkster van de afdeling A0 van de Interne Kliniek en kamer A van de Interne Polikliniek was de CZS behandeling niet zo soepel verlopen.

Ware er geen neurochirurgen geweest dan was het Ommaya reservoir nooit op z'n plaats gekomen. Aanvankelijk was het een aangelegenheid van vele hematologen en één neuroloog, doch na enige tijd vervulden ook de neurologische assistenten van de Consultendienst een rol bij de voorbereiding van de implantatie en bij de follow-up van die patienten, welke neurologische problemen hadden.

Bij het onderzoek tesamen met de collegae Bert Piers en Henk Beekhuis creëerden de laboranten van de afdeling Nucleaire Geneeskunde een vriendelijke opvang voor de patienten, toen er voor hen werkelijk van extra belasting sprake was.

Het opsporen van het neuropathologisch materiaal was in handen van Jacobien Erbrink en dit werd vervolgens kundig beoordeeld door Ineke Molenaar.

Waar zoveel disciplines bij een patientengroep als deze samenwerken, kan het niet anders dan dat alleen de inzet van ieder der betrokkenen het mogelijk heeft gemaakt deze behandeling in te voeren, door te voeren en als routine uit te voeren, waardoor tegelijkertijd de gegevens ontstonden, die in dit onderzoek gebruikt zijn. Ik ben een ieder erkentelijk voor zijn bijdrage.

De zegeningen van een multicenter trial, zoals grote aantallen patienten en significante uitkomsten bij de statistische bewerkingen zijn mij in deze studie ontgaan, maar zonder aan dergelijke positieve kanten afbreuk te willen doen, ben ik blij dit onderzoek zo intensief en langdurig meegemaakt te hebben. De verdieping van het inzicht hoe dit ziekteproces zich kan gedragen en hoe het te attaqueren groeide mettertijd. Een studie binnen een "single institute", waarbij elke patient een bekende is, heeft hierbij ontegenzeggelijk voordelen.

Als neuroloog zo op te gaan in zaken, die al gauw gezien kunnen worden als een "ver van mijn bed show", is alleen mogelijk als de uitvalsbasis iemand voldoende vrijheid laat. Mijn andere promotor Jan Minderhoud was in deze zeer genereus. Daar waar het beleid binnen de faculteit er op gericht is steeds strakker de onderzoekslijnen te definiëren, prijs ik me gelukkig een interessante neurologische weg onbelemmerd te hebben kunnen volgen.

Binnen de Neurologische Kliniek vormden de betrokkenheid van de analistes van het Liquor Lab. Lenie ter Stege en Gerda Hooites, de behulpzaamheid van Coen Dobma en de bibliothecarissen Gregory Collins en Lex Dierssen, de fotografische illustraties van J.J. Hoks en het omslag-ontwerp van Douwe Buiter essentiële schakels.

Een geruststellende gedachte is dat het thuisfront zich stabiel gedroeg, dat wil zeggen ze werden er niet anders van toen er gepromoveerd moest worden. Er behoeft nu het werkstuk klaar is dus óók niets te veranderen.

CURRICULUM VITAE

De schrijfster van dit proefschrift werd op 17 december 1939 geboren te Den Helder. Na het behalen van het diploma Gymnasium ß te Apeldoorn werd de studie Geneeskunde gevolgd aan de Rijksuniversiteit te Utrecht (1957-1964). In de jaren 1965-1971 werd te Utrecht gewerkt als consultatiebureau-arts voor zuigelingen en als keuringsarts voor de bloedtransfusiedienst en vond specialisatie tot zenuwarts met als hoofdvak Neurologie plaats in het Academisch Ziekenhuis (opleiders neurologie: Prof.dr. W.G. Sillevis Smitt en Prof.dr. A. Kemp, opleider neurochirurgie Prof.dr. H. Verbiest, opleider psychiatrie: Prof.dr. J.H. Plokker). De aantekening Klinische Neurofysiologie werd verkregen in het St. Antonius Ziekenhuis en het Militair Hospitaal (opleider dr. A.J.R. Simons).

In de periode 1972-1974 was zij als neuroloog verbonden aan het Bergweg Ziekenhuis te Rotterdam en aan het Rotterdamsch Radio-Therapeutisch Instituut / Dr. Daniël den Hoedkliniek. Wegens de werkzaamheden van haar echtgenoot verbleef zij in 1974 en 1975 te Boston (USA). Hier was zij als neuroloog werkzaam in het Jewish Memorial Hospital (Boston University), alwaar neurologische patienten langdurige en terminale zorg ontvingen, en nam deel aan diverse postgraduate courses. Van 1976 tot 1983 was zij consulent in het Psychiatrisch Ziekenhuis Licht en Kracht te Assen. Vanaf 1976 tot heden is zij staflid van de afdeling Neurologie van het Academisch Ziekenhuis te Groningen met als hoofdtaak de consultatieve neurologie ten behoeve van volwassenen en met als voornaamste interessegebied de neuro-oncologie. In het kader van dit laatste onderdeel werd in 1979 gewerkt op de afdeling Neurologie van het Memorial Sloan Kettering Cancer Center te New York bij dr. J.B. Posner. Zij is voorts lid van diverse multidisciplinaire werkgroepen, o.a. de Pijn-werkgroep en de werkgroep Wervelfracturen in het AZG en de Landelijke Werkgroep Neuro-Oncologie. In 1987 werd zij aangesteld als consulent bij het Integraal Kankercentrum Noord.